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PRESIDENTIAL ADDRESS*

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I DESIRE first to express my sincere thanks for the wholly unexpected honor you so graciously conferred upon me a year ago by choosing me to be your President. On the whole, my professional life from my student days to the present, despite the necessary hardships, unending tasks, long hours, and many disappointments, has been pleasant and gratifying and I have enjoyed it.

A year ago, when I was beginning to relax, stand on the side lines and take it easy, you did me the greatest honor that one of our profession and specialty could desire, by making me your President. I thank you, one and all, from the bottom of my heart.

In considering the subject to discuss with you in this address, it seemed to me it might be worth while to evaluate some of the historical developments in the field of cancer of the cervix, as revealed in the *Transactions* of this Society. To add a personal touch, I have combined this with a brief study of the records of 400 patients with cervix cancer still in the active files at Memorial Hospital, who were treated for their disease with radium or radium and x-rays during the years from 1921 to 1942, when I was in charge of the Gynecological Department.

Even a cursory review of our annual *Transactions* seems to reveal that cancer of the cervix is a recurrent and persistent problem constantly under discussion. The problem on the whole has not had to do with the etiology of the

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disease, which, in common with all forms of cancer, still is obscure, despite many theories and much research. The question has been, and still is, what to do with each individual case of cancer of the cervix, when it is recognized.

It is one of the most dread and frequent forms of malignant tumor and, in the untreated patients, the growth tends to run a rapid course. The great majority of such patients die within two years and many within one year; practically all within three years.

How prevalent is cancer of the cervix? It is estimated that 60,000 women are under treatment in the United States during any one year for this disease. Each year about 13,000 women die from it. It is difficult to get the mortality rate for cancer of the cervix alone, as it is included with cancer of the uterus in the Vital Statistics, but it is interesting and encouraging to know that the death rate for cancer of the uterus has declined appreciably from 29.9 adjusted rate per 100,000 female population in 1935 to 22.4 in 1949. This, I would be inclined to assume, could be a result of earlier diagnosis and more prompt and efficient treatment.

It must be realized that gynecologists were pioneer abdominal surgeons, but from 1876, when our Society was organized, to 1891, such surgery was in its infancy. The attempt to remove the diseased cervix was largely restricted to the vaginal approach and consisted in its amputation by the Galvano cautery, according to the method of John Byrne of Brooklyn, or by sharp cutting instruments, such as the knife and scissors, plus cauterization, as advised by Baker of Boston.

The following 25 years, from 1891 to 1916, represented great advances in the technique of abdominal and pelvic surgery. Extensive surgical procedures were developed by Clark in this country and Wertheim in Europe, directed toward the removal of the involved tissues of the broad ligaments as well as the pelvic lymph nodes at the same time that the uterus, tubes, and ovaries were removed. Those operations were long and extremely difficult. There was marked blood loss, with resultant severe shock to the patient, considerable morbidity due to injuries, especially to the ureters, bladder, and rectum, as well as frequent coincident severe infection of the surgical field. Most serious and important of all other considerations, the operative mortality due to surgical shock and infection was high.

In those days, we know, anesthesia was crude. There were no blood transfusions to combat shock, nor did the surgeons have the help of sulfonamides or antibiotics to combat infection. The situation was serious for the patients and the gynecologists. To quote such an able surgeon as Peterson, who at the 1916 meeting said: "Unfortunately added experience has strengthened my belief that the extended operation for cancer of the uterus is exceedingly dangerous, always attended by a high primary mortality, and it is no operation for inexperienced hands. No one will be more glad to discard the radical abdominal method than I will, if I can be shown that more patients can be ultimately cured by less dangerous methods."

The x-ray was discovered by Roentgen in 1895 and radium by Pierre and Marie Curie in 1898. Three years later Dr. Becquerel of Paris discovered

the effect of radium rays on human tissues. Early in this century, therefore, radium rays were known to have an inhibiting or destructive effect on human tumors, especially the malignant variety.

The first institution in this country established exclusively for the care of cancer patients was the New York Cancer Hospital, opened in 1887. Clement Cleveland, one of its first surgeons, a distinguished gynecologist and a Fellow of our Society, in whose memory the Clement Cleveland medal is awarded annually by the New York City Cancer Section of The American Cancer Society, said at our meeting in 1889: "The majority of cases of cancer of the cervix admitted to this Hospital have such extensive disease that treatment is essentially palliative only."

In 1899 this institution became the General Memorial Hospital for the treatment of cancer and allied diseases. In 1902 the Hospital received a gift of $100,000 from Mrs. Charles P. Huntington for the establishment of a fund for cancer research. This, I believe, was the first cancer research fund in this country and gave a new impetus to treatment and research.

In 1913 an affiliation took place with Cornell University Medical School and James Ewing, Professor of Pathology, became President of the Medical Board of the Hospital.

In 1914, James Douglas, Ph.D., who had become interested in cancer research, particularly in connection with radium, besides money and other gifts, gave 3½ grams of radium to the Hospital. Thus, in 1914, Memorial Hospital became one of the first hospitals in this country to utilize radium in the treatment of cancer.

In 1921, I took over the Gynecological Service from Harold A. Bailey, one of our Fellows, who had organized it in 1915. Those were, of course, pioneer days in radiation therapy. Treatment was restricted to the use of various types of locally placed applicators containing radium salts, or radon, the emanation collected from the element.

In 1916, Kelly and Burnam made their first report to this Society on their personal experience in the treatment of 327 cases of cancer of the cervix, uterus, and vagina with radium. Their conclusions were: "The earlier the case is treated, the better are the results of radiation." Kelly was as yet unwilling to agree with Döderlein that radium should supersede operation in all the early operable cases because, "there are certain squamous cell cancers in the cervix where, as yet for reasons unknown, radium does not cure." How true that observation was, we all realize. These cases now are designated as radiation-resistant tumors. It is quite possible that the recent cytological studies Ruth Graham is doing will permit these radiation-resistant tumors to be identified early in the course of radiation therapy, thereby saving valuable time and permitting more prompt resort to operation, as in such cases operation would seem to be superior to irradiation.

In 1917, Bailey made his first report from Memorial Hospital on 120 cervix cancer patients. He emphasized the importance of cross-firing on the lesion, a method the value of which later became fully recognized and adopted, whenever possible.

In 1918, Burnam emphasized that metastatic growths are likely to be more resistant to radiation than the primary tumor, all of which has been amply verified since.

About this time, the cases were divided into three clinical groups, early, borderline, and advanced, according to the gross extent of the cancer in and about the cervix. It was thought, however, the early cases, and some of the very favorable borderline cases might do better if operated on. The crux of the matter was a realization that even in many of the early cases, pelvic lymph nodes were involved in metastatic cancer, as had been demonstrated by Sampson in 1906, and it was doubted they would be controlled by radiation.

About 1920, radiation therapy definitely replaced surgery throughout the world in all cases of cancer of the cervix, regardless of the clinical setting—early, borderline, or advanced, with the exception of those treated by an occasional able surgeon like Bonney in England, who continued to operate on his patients. In Europe, two outstanding institutions had already established leadership in the field of radiation research and treatment for malignant diseases: The Radiumhemmet of Stockholm and The Radium Institute in Paris.

When I took over the Gynecological Service at Memorial Hospital, we had about 2½ grams of radium in solution, from which the emanation was collected in capillary glass tubes and placed in applicators of various types and strength, running from tiny glass seeds, platinum and brass capsules, up to large lead-lined so-called "vaginal bombs."

Through the years from 1921 to 1942, we had recorded in our admission books about 2,800 patients with cancer of the cervix. Of interest to me are the records of close to 400 of these patients, who still report to the Hospital Follow-up Clinic annually for examination. They have been free from active evidence of cancer for ten to thirty years. All of them have been treated by radium or radium and x-ray only. Some, because of advanced age and physical incapacity, report by letter. Many of these patients now are in the seventh, eighth, and ninth decades of life, and among the 400 patients there have been only nine new primary malignant tumors of other organs, all of which have been treated surgically and apparently with success. Two additional patients had early Stage I lesions, histologically described as epidermoid cancer, Grade 2, with adenoid features, which responded splendidly to radium and x-ray, and each was entirely free from evidence of disease for ten years, then developed an enlarged uterus, which was surgically removed and revealed a new primary tumor of the uterine body, designated adenocarcinoma, Grade 4, with sarcomatous features, as well as extensive parametrial and lymph node metastases. One wonders if these patients would not have been protected from their second primary cancers, if the uterus had been removed for the first cancer, which is an argument for those who prefer surgery.

I think it may be significant that there are 60 Italian women in this group, which seems unduly high for that nationality. In percentages, the 400 survivors divide up about as follows: 43.8 per cent early, 33.6 per cent borderline, 22.6 per cent advanced. For the record, may I here say, each and every

case included in this review has been histologically proved to be cancer. In fact, in the early years most of the slides were seen by James Ewing. It is interesting that in each year, beginning with 1920, when Bailey was still in charge, there are survivors. No year draws a blank. Of the three survivors from 1920, two cases were instances of recurrent cancer in the vaginal vault following hysterectomy for cancer of the cervix. It may be worth while to review the primary case briefly.

A. H., aged 52 years, had an ulcerating excavating lesion, involving the entire circumference of the cervix along and surrounding the cervical canal, extending upward toward the internal os, no gross evidence elsewhere. Diagnosis: cervix primary, early. Biopsy: squamous cancer. Treatment: Platinum tandem two tubes within the cervical canal, 3,165 mc. hr., small vaginal bomb, three positions, total dose 1,537 mc. hr., no external irradiation. She has remained well 33 years and is now 85 years old. In these three cases, since treatment was limited to vaginal applications of radium, we must assume there were no involved pelvic lymph nodes and little, if any, parametrial disease.

Why have these 400 patients survived? What happened to cure them? Was the disease more limited than was thought? Did they develop from the adrenal or pituitary or some other source an enzyme or some substance antagonistic to the cancer cell, which destroyed its further activity? Does the presence of dying and dead cancer cells from irradiation stimulate the defensive forces of the body to the production of a protective mechanism, which inhibits in many cases further growth of cancer cells, somewhat as a foreign protein substance? Frankly—we do not know. It is extraordinary to review the records of patients still alive and well, treated 25 or 30 years ago with radium only. All of them were referred by their family physicians with a clinical diagnosis of cancer of the cervix, so there must at least have been obvious gross evidence of the disease. They were examined at the Clinic by several specialists in conference, who decided the clinical stage of the disease. One or more biopsies were made of the suspected area and, finally, the report was received from the laboratory, verifying the diagnosis of cancer. So we know, without any doubt, that these women suffered from cancer well established in the cervix. Moreover, it was infiltrating cancer, as in every instance an ulcer was present with varying degrees of enlargement of the cervix.

In the borderline and advanced cases, there is in the records evidence of palpable disease, described as extending beyond the cervix to other structures in the pelvis. The attack on the disease in many of our first cases was limited to the vaginal and intracervical application of radium. Very little effort was made to control the disease, which was spreading to other parts of the pelvis, as there were really no facilities with which to do this.

When I took over the Service, I found that many of the patients were not receiving external irradiation, as the radium block applicator tied up so much radium, it interfered with the requirements of other services. After discussing the problem with our Physics Department, we switched from the radium

block to x-ray for external treatments. In those days, 1922, only low-voltage x-ray was available, but this gave more effective irradiation than had been obtained from the radium-block. I have read with great care the records of these 400 patients, seeking a lead of any kind as to why they did well. All of them responded promptly to irradiation and within two to three or four months each one was said to be free of evidence of disease. This immediate favorable response may be important as a prognostic indicator.

There were but three or four instances in the group of later-appearing metastatic lesions. With one exception, they were in the vagina and responded favorably to surface irradiation with radium. The exception was quite interesting. The patient, 46 years old, had been treated with x-ray and radium for a primary borderline, Stage 2, cancer of the cervix. Its histologic structure was anaplastic epidermoid cancer, Grade 3. The response to irradiation was entirely satisfactory and all evidence of cancer quickly disappeared. Three years later a large node appeared beneath the left sternomastoid muscle, about one inch below the ear. The node had been present two weeks; aspiration biopsy was done and the laboratory report was epidermoid cancer consistent with cervix primary. The node, including the left neck, was irradiated with high-voltage x-ray for three weeks. It entirely disappeared within three or four months. Twelve years have elapsed and no other lesions have developed. This would appear to be a specific instance of a metastatic lymph node regressing under x-ray therapy. But, you must realize, it was pinpointed in the treatment. Lady Luck was with this patient in locating the metastasis where it could quickly be identified and also be adequately treated.

There were 29 cervical stump cases which constitute about 8 per cent of the survivors, which seems to me to be a high percentage of such cases. The patient who has lived longest had an advanced case, treated nearly 25 years ago. All the survivors with stump cases, histologically had epidermoid cancer. There are three or four patients grouped as very advanced Stage 4, in which treatment was to have been palliative only, according to the records. However, they have survived 14 to 19 years and still are free from evidence of cancer. It hardly seems reasonable to assume that there was no parametrial or lymph node cancer in any one of these. If there was, what became of it? They were treated in the middle and late 30's, when we were giving multiple divided-dose roentgen therapy to the parametrial areas.

Ninety-eight of these patients have been living and well 20 to 30 years since treatment. Fifty-two of these were regarded as favorable for cure with the cancer apparently limited to the cervix. In 23 cases the cancer appeared to have spread beyond the cervix, and in another 23 cases it was regarded as advanced involving the broad ligaments and the vagina.

The treatment of the primary cancer in the cervix with radium in all these 98 cases, 20 to 30 years ago, I think was excellent, and as good as is done today. Actually, I would not change it. The treatment of the parametrial and metastatic cancer in the pelvic lymph nodes, however, was crude and inade-

quate, because the facilities and x-ray equipment of recent years were not available when these 98 patients were treated previous to 1933. Since 23 of these cases were classed as Stage 3, advanced cancers, we must conclude that either our judgment as to the extent of the disease was in error, which is, of course, quite possible, or that the outlying disease was radiation sensitive and disappeared as a result of radiation therapy, directly or indirectly, which I do not find difficult to believe, as over the years I have seen so many cancers disappear under irradiation dosage which would be regarded as inadequate according to known standards, that I believe frequently cancer disappears, because of some chain of events started by a reaction to irradiation, antagonistic to the growth of the cancer cell even beyond the field of direct radiation effect.

Radiation therapists today are constantly improving their technique and their therapeutic facilities. Witness the significant increase in percentage of 5 year cures reported by McKelvey in 1949, which it seems might be attributed to two factors: *one,* a fixed plan of irradiation with x-ray and radium; and *two,* hospitalization of the patients during the entire course of treatment, which permitted them to be fed, nursed, and rested, just like the patient who undergoes surgery. Always, I have insisted that the woman who receives a full course of irradiation for cancer of the cervix has undergone the physical and mental stress and strain equivalent to that associated with a major operation. As far as I know, McKelvey and his associates are the first to recognize the need of doing something about it in a practical and thorough way and are to be commended for it.

For the past ten years there has been a great furor about carcinoma in situ. Its recognition is now an established diagnostic procedure by means of stained vaginal smears verified by tissue biopsy, just as in cancer of the cervix. It has been accepted as Stage *Zero,* a new stage in the International classification of the stages of carcinoma of the uterine cervix. It is not histologically invading cancer and does not require the radical surgical or irradiation therapy of cancer for its control. There are many cases on record where the patient in the child-bearing age has had this lesion removed by partial trachelectomy, subsequently conceived, and been delivered normally without recurrence of the lesion, or the development of cancer in the cervix.

Much of the brilliant and enlightening discussion dealing with this controversial topic has occurred on the floor of this Society and we are greatly indebted to Te Linde, Hertig, Carter, McKelvey, and their associates for splendid contributions to this subject.

During the last ten years, improved operating-room facilities have increased greatly our ability to subject patients safely to long and exhausting surgical procedures heretofore not possible. Once again, as fifty years ago, the surgical instinct has been aroused in the gynecologist, and the pendulum has taken a swing toward surgery in cancer of the cervix. The swing, however, fairly well controlled, may be regarded as still in the developmental stage, but much of real value already has been learned. There no longer is any doubt, with

modern operating-room facilities and well-trained and experienced gynecological surgeons, that many cases of cervix cancer can be operated on to the patient's advantage and without undue risk. It seems to me the only operation to be considered is the one described by Meigs as radical hysterectomy with bilateral pelvic lymph node dissections. Today, it must be regarded as a successful surgical procedure without the high mortality and complications that plagued our distinguished predecessors. We are not better, or more skillful surgeons today, than were our predecessors, but we have better tools and facilities to aid us in traveling the same surgical road they tried to travel.

Meigs and his associates deserve credit for the renewed interest in the surgical approach and for carrying out persistently his first 100 personal operations, which required 7 or 8 years to accomplish and represent a splendid piece of successful experimental surgery. The report of his first 100 cases now is available. There was no mortality and 75 per cent of the patients have survived five years. Even though this was a carefully chosen group of patients, 66 being Stage 1 and 34 Stage 2, nevertheless, the 5 year salvage was 75 per cent, which must be regarded as excellent.

In my opinion, it is tops and will be difficult to equal or surpass surgically, without restricting the choice of patients to Stage 1 cases. The moment you mix the stages, and choose patients from Stages 2, 3, and 4, the cards are stacked against you and the surgeon cannot hope to maintain a 75 per cent level of 5 year salvage.

Why do I say this? The answer is that the incidence of metastatic pelvic lymph nodes is too high in all but the Stage 1 cases to permit a 75 per cent level to be maintained even without mortality. Meigs had 23 per cent of positive nodes in his series, of which one in four survived 5 years. Only 18 per cent of his Stage 1 cases were associated with positive lymph nodes, suggesting they were well selected; whereas 32.3 per cent of the Stage 2 had positive nodes, which corresponds more closely to Sampson's studies and Bonney's and Wertheim's operative experience. Wertheim found that the disease recurred in all his cases in which lymph nodes were involved at operation, so he regarded their removal as of prognostic value only.

Bonney reported regional lymph nodes carcinomatous in 42 per cent of his operable cases; that about one in five patients survived 5 years and the operative risk in these cases was 20 per cent as against 10 per cent when there were no regional lymph nodes involved.

It is significant that in Meigs' Stage 2 cases with lymph node metastases, only one out of eleven patients survived 5 years. So it would seem reasonable to assume that if more Stage 2 or Stage 3 cases are treated surgically, the total salvage will fall.

Therefore, as I have already implied, surgery will have to be restricted for the reasons given to a limited number of carefully selected cases.

What about irradiation for cancer of the cervix? Well, we know that it does cure the disease. I have reported to you, today, some 400 patients who have lived 10 to 32 years since irradiation for cervix cancer. I also sincerely

believe there are many more specialists, clinics, and hospitals qualified to treat all cases of cervix cancer with irradiation to the patient's advantage than ever will be qualified to treat them surgically. The reason is simple: With the exception of a few radiation-resistant cases, every case, except the most hopelessly ill, or advanced, can be benefited, palliated, or cured by irradiation, whereas surgeons are limited to the most favorable cases, recognized early, and there are too few of these cases scattered over the country to permit the difficult technique of this operation to be acquired by many surgeons. The result, I fear, and I regret to say, will tend to be inadequate and incomplete surgery for many of these patients.

What we most earnestly want to do is to cure the cases that can be cured, and to palliate the others. We have every reason to believe that irradiation methods can and will be improved.

This review of my cases gave me the impression that when cancer recurred in the cervix a year or more after full irradiation with radium and x-ray, it would be preferable in most instances to treat these late cervical recurrences by simple total hysterectomy without parametrial and lymph node excision. This procedure will get rid of the active cancer in the cervix and protect the patient from any annoying discharge and bleeding while she lives. If parametrial disease and lymph node metastases are present, the radical operation would only be temporarily palliative at best and the risk of incapacitating complications would be grave. I consider the simple hysterectomy more desirable than reradiation in late local recurrences.

In closing, may I say, it seems to me with modern methods of irradiation and our present advanced surgical procedures, we have progressed about as far as we can hope to go in establishing a cure for cervical cancer, but it is not discouraging. Great and amazing progress has been made in the last twenty years in both fields.

There will always be incurable cases, just as long as there is cancer. We are just like fire fighters—we are called only after the fire has started and what we accomplish depends on how limited the fire is when we arrive, how inflammable the materials are that are involved, and how experienced and competent we are in the use of the tools available to fight it.

It seems to me our greatest hope is that research will ultimately produce some hormonal substance, or substances, antagonistic to the chaotic growth of cancer cells, so that their activity will be inhibited and that by simple medication alone they will return to normal.

121 East 60th Street

OPTIONAL NURSERY FACILITIES FOR THE CARE OF MOTHERS AND NEWBORN INFANTS*

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THE purpose of this presentation is to report observations from a program of care for mothers and the newborn in which optional accommodations were available to all patients. These findings cover a five-year period of study from April 1, 1948, to April 1, 1953, during which time 14,309 mothers were delivered of 14,438 infants. While some of the philosophy of rooming-in is incorporated in this plan, the experiences to be reported here take the form of a comparative evaluation of a variety of mother-infant facilities.

When the President of the University and the Dean of the School of Medicine, late in 1944, asked that we work with the architects on blueprints for the maternity division of the George Washington Hospital we had an opportunity to develop a new nursery plan to take the place of the usual large centralized nursery. Past experience with the mass management of infants in large nurseries had proved it to be medically unsafe and emotionally unsound. The long multiple-wing floor plan seemed to lend itself admirably to decentralized nurseries (Fig. 1).

As plans progressed, nurseries became the centers around which the mothers' rooms were arranged. A wide choice of nurseries was provided, ranging from eight-crib nurseries in the same wing as the mothers' rooms, to four-crib nurseries between double rooms, to individual nurseries in mother-infant suites. Different mother-infant accommodations were designed for separate units of the maternity floor to permit a comparative study of the various facilities. Large windows were incorporated as a feature of each nursery to permit a clear view of infants at all times.

For example, one unit contained eight single rooms each with an individual nursery. A control wing of similar size contained an eight-crib nursery and eight detached single rooms for the mothers. In the long center area a series of four-crib nurseries, each flanked by double rooms, made up another study area. Three wings contained eight-crib nurseries with near-by single, two-, or four-bed rooms for the mothers. In order to have a continuity of infant care either in the nursery or at the bedside of the mother mobile bassinets were incorporated in the preliminary planning. The bassinet was designed for safety and universal convenience. For the comfort of the mother and as a labor-saving device for the nurses, a self-adjusting type of hospital bed was provided.

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All nursery-mother units were planned to permit a minimum of corridor exposure for the infant; to facilitate nursing care; to protect against cross infections; to reduce noise; and to allow mothers, fathers, and relatives to see their healthy infants with freedom.

In the care of mothers and infants it was thought that attempts at antiseptic techniques had developed far beyond the science of human relations; that large nursery units were hazardous; that the hospital should not only substitute for the home during the birth of an infant, but also serve as a center for family education, and that healthy mothers and healthy infants should be permitted to continue a normal biologic relationship during those early days of life in the hospital. It was further believed that maternity facilities should be arranged so that maximum scientific safety might be provided in an optimistic environment where the family would be as free as possible from any of the apprehensions of hospitalization.

Nursery Details*

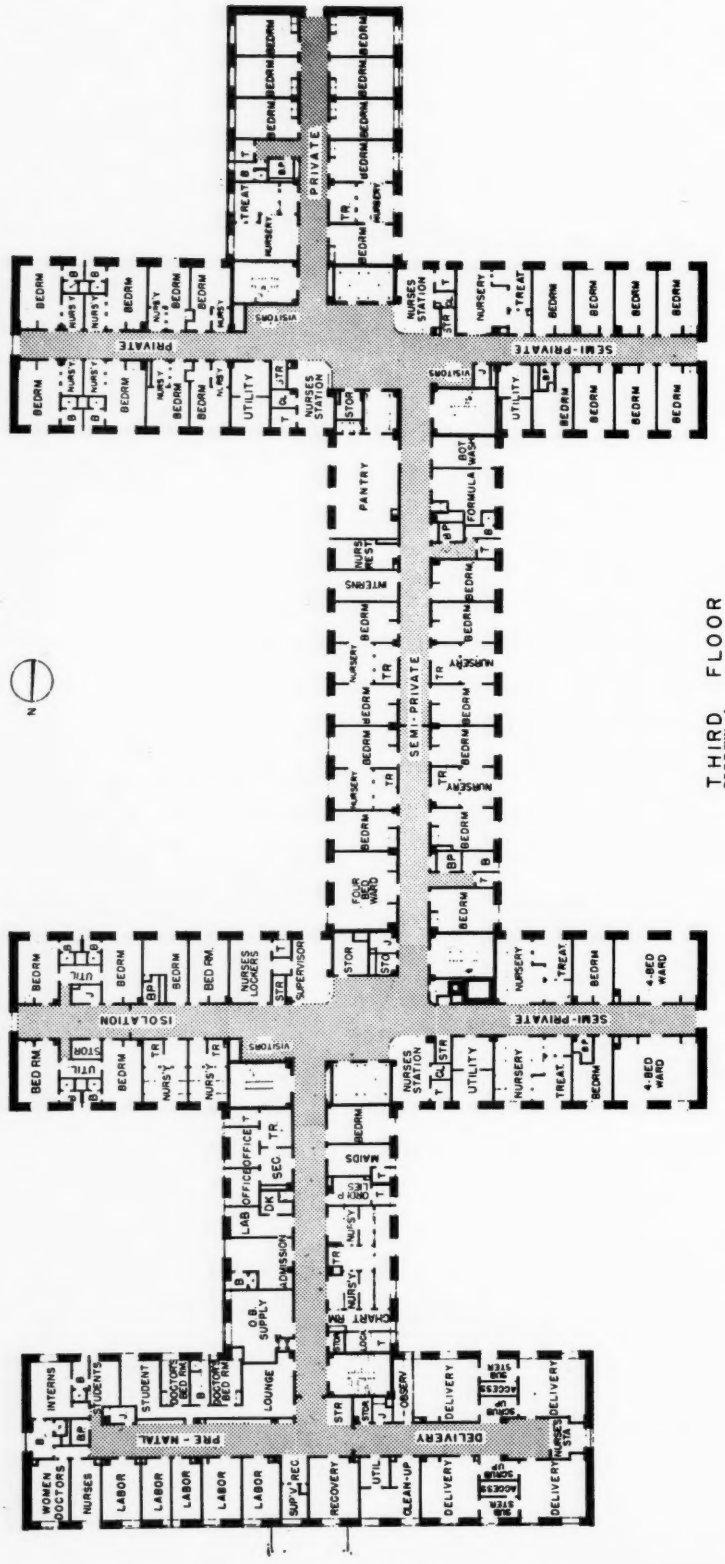
Premature Nursery.—Infants that weigh less than 5½ pounds and those with evidence of immaturity are cared for in the premature nursery, a separate and fully equipped unit adjacent to the delivery suite. Since mothers participate very little in the early care of their premature infants, a discussion of this group of patients would seem unrelated to our subject. However, premature infants and their parents need unusual attention and care. Freedom to observe the premature infant is of value to the family. With all partitions of clear glass and with large view windows on the corridors, the premature infants are under the constant observation of the nursing staff, the physicians, the parents, and visitors. Having these small babies in view has been an added stimulus for the nurses to give individual attention, not only to the infants, but to the parents as well. Prior to discharge, the nurse gives the mother individual instruction on how to handle and feed the infant.

Eight-Crib Nurseries.—The largest nursery designed for normal infants has space for eight cribs. Twenty-five square feet of floor space are provided for each infant. Partitions placed along the outer walls make the center area of the nursery free. All infants can be viewed from the corridor through a large window. Each eight-crib nursery has adjoining treatment and chart rooms with the upper walls of clear glass. Eight-crib nurseries are located in wings near one-, two-, and four-bed rooms for mothers.

Regardless of the accommodations, the mother may have her infant with her as much or as little as she wishes except during visiting hours at which time all infants are in the nurseries. Having the infant at the bedside of the mother or in the full-view nursery has permitted the wider use of nurses' aides. Graduate nurses have had more time to teach the mothers the essentials of baby care.

Four-Crib Nurseries.—Provisions were made for twenty mothers to have their infants in four-crib nurseries placed between double rooms. An observa-

*Floor plans and equipment details for each type of nursery were published in *Modern Hospital* (Chicago) 65: 46, 1945.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(MATERNITY)
THE GEORGE WASHINGTON UNIVERSITY HOSPITAL
FAULKNER KINGSBURY & STENHOUSE – ARCHITECTS
WASHINGTON, D C

Fig. 1.

tion window between nursery and room permits the infant to be in close view at all times. At visiting hours, the infant may be seen by the family from the mother's room, thereby saving nurse hours. Floor space occupied by two four-crib nurseries is exactly the same as for one eight-crib nursery. The small chart and treatment rooms are convenient, but not essential. Partitions help individualize space, but are not necessary.

Individual Nurseries.—Individual nurseries were arranged with corridor viewing windows which permit the nurse to observe all eight infants without disturbing the mothers at night. An infant is placed in an individual nursery only after his air passages are clear, after he reacts normally, and after the mother is fully awake and rational. The mother has privacy for her infant as well as for herself. The husband has freedom to participate in some of the early care of the infant and to observe the developmental characteristics of his son or daughter.

Observations by the Staff

Survival Statistics.—In the past, obstetric progress has been measured by maternal and neonatal mortality rates. Neonatal mortality is a much more delicate index of obstetric care than is gross maternal mortality. With both mother and infant there is a wide and somewhat immeasurable margin between survival and health.

From April 1, 1948, to April 1, 1953, there were 14,309 patients delivered in the George Washington University Hospital. Two of these mothers died. One patient died of a ruptured renal aneurysm which occurred in the last weeks of pregnancy. The second patient died of acute poliomyelitis and was delivered post mortem of a dead immature fetus.

Of the 14,438 infants delivered, 153 were stillborn. Out of the 13,706 living infants whose birth weights were more than 5 pounds, 8 ounces, 64 died, giving a survival rate of 99.53 per cent. There were 37 neonatal deaths among the 488 infants with birth weights of 3 to 5 pounds, 8 ounces, giving a survival rate for this group of premature infants of 92.5 per cent. Neonatal deaths for infants that weighed 3 pounds or less were 66 out of 91, for a survival rate of 27.5 per cent.

While these figures are of limited statistical value they indicate that the preservation of life for mother and infant can be accomplished in current hospital obstetric practice. Similar survival figures are being duplicated in both large and small maternity services throughout the United States today.

Infection.—There has been no spread of infection except in the premature nursery. On two occasions thrush has involved a total of six infants. Infants who stayed at the bedside of the mothers have shown little evidence of diaper rash and other skin infections. Infection has not been a factor of concern in this program of mother-infant care.

Crying.—A rather interesting observation relates to the crying habits of infants. Previous experience with infants congregated in large nurseries, and particularly where four-hour feeding schedules were maintained, showed that the crying of a few infants stimulated the others to respond in a similar manner. After prolonged periods of crying hunger was more difficult to satisfy.

One of the very noticeable features of the decentralized nursery plan has been the unusual quietness on the part of the infants. Seemingly purposeless crying occurs infrequently. The majority of infants are permitted to feed whenever they are hungry. Within reason, an elective plan of feeding permits the infant to develop a schedule in keeping with his needs. If his hunger is satisfied, he cries less and the mother is more inclined to be content.

In addition to satisfying hunger there is another advantage to the infant at the bedside during a greater part of the day. He becomes accustomed to the everyday noises of adult living such as telephones, radios, and conversations. Many mothers have reported that the baby she has had in her room at the hospital has not been disturbed in his sleep by the usual noises at home.

Infants in View.—View windows have been found to be an important part of each nursery. In their transparent plastic bassinets infants can be seen at all times. Preliminary responses of the nurses to carrying on their work in view of the passing attending staff and the always interested parents were not entirely favorable. However, as time went on the nurses began to take an increasing pride in their activities. Now, nursery bottles are not propped; crying babies are attended; nursery aides are used more efficiently, and critical emergencies have been discovered immediately.

Nursing Time.—The ratio of mothers and infants per nurse is the same in all of the various accommodations, i.e., about 8 infants or 4 mothers and 4 infants for each nurse. At night this patient-per-nurse ratio is increased about 50 per cent. With mothers feeding, changing, and otherwise participating in the care of their infants, nurses are freed to teach the mothers methods of newborn care. In the individual mother-infant accommodations and usually in the four-crib nursery facilities, the same nurse cares for mother and infant. During the first three or four days, an inexperienced mother may require more than average nursing time. But if successfully taught, this same mother will assume an increasing responsibility and efficiency in the care of her infant.

Costs.—Hospital administrators, the public, and physicians must realize that adequate infant care is expensive. The newborn is an individual admitted to the hospital by way of the delivery room. Of all people who enter a hospital for any reason, the newborn is the most sensitive to his hospital environment. Safeguards must be provided for him in the form of sufficient nursery space and proper nursing care. The procedure of permitting the mother and infant to be together in the hospital is no more expensive than any other system of adequate care. Hospitals should receive enough income from nursery charges to provide satisfactory services for their infant patients. Large and overcrowded nurseries will persist until these charges equal the costs of infant care. In dividends of physical and mental health the mass management of infants in large nurseries separated from their mothers is not economical.

Observations by the Patients

In order to obtain the patients' point of view regarding this plan of mother-infant care, 2,244 questionnaires were sent out to parents whose infants

were normal and whose hospital stay in 1952 had been uncomplicated. There were 1,653 usable returns. Realizing that any questionnaire survey can be misleading, an effort was made to have the parents return an unsigned evaluation of the services which they received. A short introductory letter from the Departments of Obstetrics and Pediatrics of the George Washington University accompanied the questionnaire. A separate United States postage stamp issue was used on the return envelope for identification of each of the seven types of accommodations surveyed. Unfortunately, a few of the questionnaires went to collectors who replaced the special issue stamps with regular postage, thereby removing the method of identification of the facility used. These returns had to be discarded.

The questionnaire was as follows:

PLEASE CIRCLE YOUR ANSWER

Were the accommodations you requested available at the time of your admission to the hospital?	YES (77%) NO (23%)
If NO, when were you transferred to the room you requested ____ day.	
Was your room satisfactory?	YES (99%) NO (1%)
Was your nursery arrangement satisfactory?	YES (96%) NO (4%)
Did you visit the hospital for a tour of the maternity division before your admission?	YES (16%) NO (84%)
Was the baby born in 1952 your: 1st (39.2%); 2nd (32.8%); 3rd (15.6%); 4th (8.3%); or 5th (or more 4.1%) baby?	
Have you had a baby at the new George Washington University Hospital before?	YES (27%) NO (73%)
If YES, did you have the same room and nursery arrangement with your last admission?	YES (53%) NO (47%)
What nursery facilities would you select next time? INDIVIDUAL NURSERY (13%); 4 CRIB ADJACENT NURSERY (41%); 8 CRIB NURSERY APART FROM ROOM (46%).	
Did you breast feed the baby?	YES (52%) NO (48%)
If YES, for (2 wks—96%) (4 wks—75%) (8 wks—51%) (12 wks—40%) (24 wks—9%) weeks.	
Did you have your baby in the room with you: AS MUCH (87%); MORE (9%); LESS (4%) than you liked?	
Did you obtain adequate rest in the hospital?	YES (70%) NO (30%)
If NO, please explain.	
Was your nursing care: EXCELLENT (50%); ADEQUATE (45%); INADEQUATE (5%)? If INADEQUATE, please explain.	
Did you feel well acquainted with the baby by the time you left the hospital?	YES (96%) NO (4%)
Do you feel that your hospital acquaintance with your baby helped you during your first few weeks at home?	YES (93%) NO (7%)
COMMENTS:	
SUGGESTIONS:	

The first two questions regarding the availability of accommodations were of concern primarily to the hospital administration.

With the maternity service averaging 86 per cent occupancy there were times when it was not possible to place patients immediately in the type of facility they desired (Fig. 2). Even though 23 per cent of the patients were placed in accommodations which they had not requested, it is surprising that 99 per cent of patients found that their room arrangements were satisfactory (Fig. 3). It is even more gratifying to learn that 96 per cent of the patients found the nursery arrangement satisfactory (Fig. 4).

For the past four years biweekly introductory tours of the maternity division have been conducted by the nursing staff. Patients and their husbands are invited for a preliminary visit to the maternity division. The various accommodations are explained along with procedures of admission and the cost of the various arrangements. Sixteen per cent of all the patients availed themselves of the opportunity to preview the maternity floor in 1952. The majority of the other patients were already acquainted with the hospital facilities.

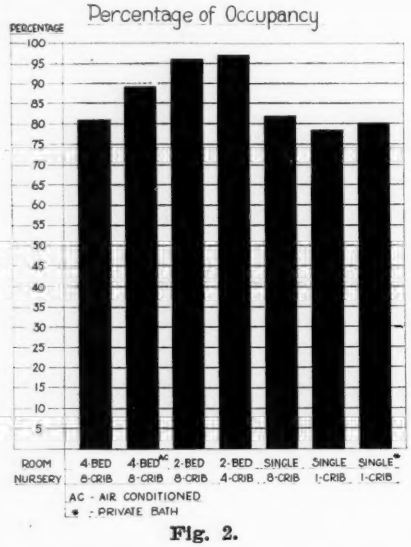


Fig. 2.

It is interesting to evaluate the birth order of the child delivered in 1952, in relation to the accommodations selected by the parents (Fig. 5). Many families chose individual mother-infant accommodations with their second, third, and fourth infants.

In response to the question of what nursery facilities the patient would select the next time, 13 per cent would want an individual nursery; 41 per cent a four-crib nursery in proximity to the room, and 46 per cent would select an eight-crib nursery separate and apart from the mothers' rooms (Fig. 6).

A series of periodic surveys have all shown about the same percentage of breast feeding. In 1952, 52 per cent of the mothers breast fed their infants (Fig. 7). It is a rather general feeling among the obstetricians and pediatricians on the Staff that a mother should have some freedom of choice

in the way she elects to feed her infant. No one demands that every mother try to breast feed. Practically all members of the Staff encourage the mother who wishes to nurse, and there are relatively few professional opponents of breast feeding. Regardless of the method the mother chooses to feed her in-

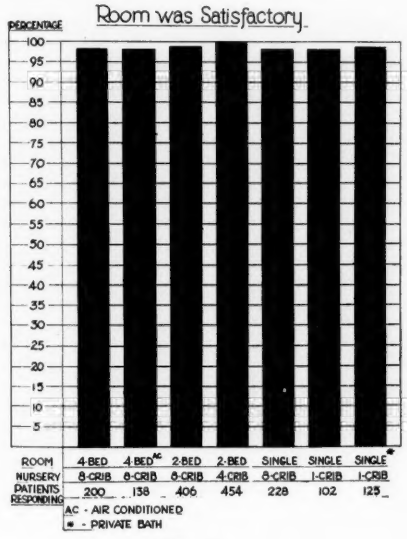


Fig. 3.

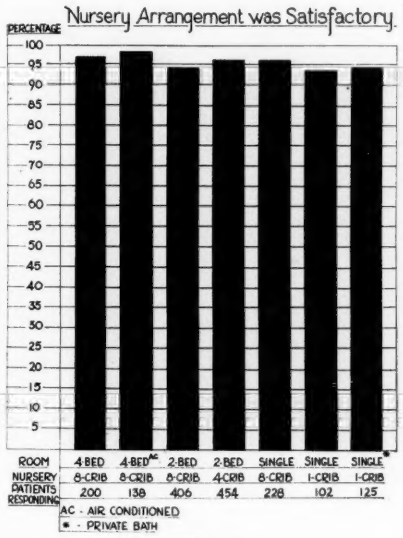


Fig. 4.

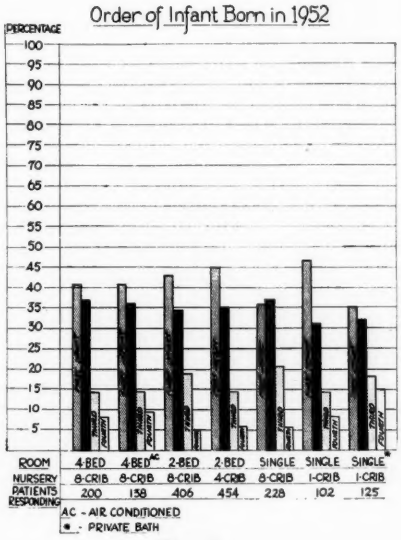


Fig. 5.

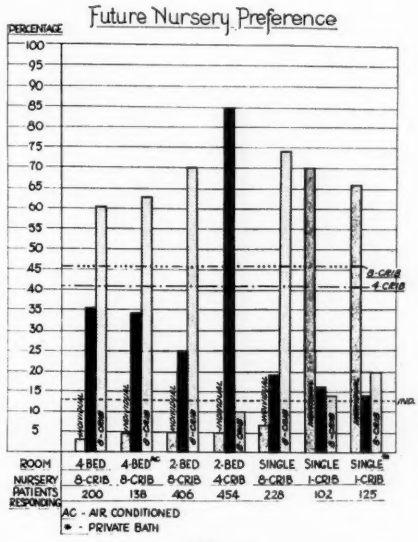


Fig. 6.

fant the nurse's duty is to help her establish a healthy approach to feeding habits. Many mothers have expressed appreciation at the ease with which breast feeding is made possible with the infant at the bedside.

In any system of mother-infant care it is difficult to meet the individual needs of all. Nevertheless, 89 per cent of the mothers felt the infants were at

the bedside about as much as they liked (Fig. 8). Nine per cent of mothers thought that the baby was in the room more than they desired. On the other hand, 4 per cent were of the opinion that the baby was in the room less than they liked.

Adequate rest in the hospital is a disturbing problem. That 70 per cent of women felt they obtained adequate rest was surprising. However, particular attention was directed to the 30 per cent who felt that they received inadequate rest in the hospital (Fig. 9). Some of the reasons recorded were: too many visitors, visiting hours too long, noisy roommates, too many phone calls, floor waxers too noisy, and, in general, too many interruptions. Few patients recorded the infant as a disturbing feature in their hospital rest. The type of mother-infant accommodation had limited influence on the patient's rest.

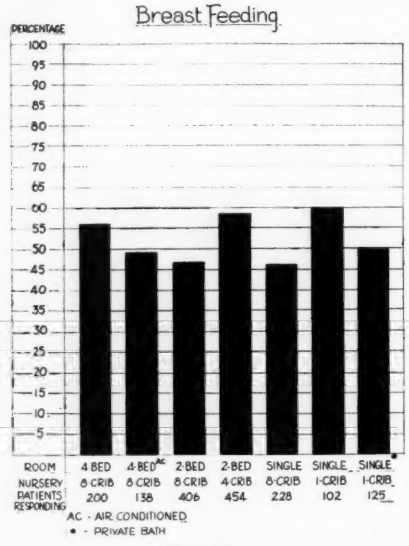


Fig. 7.

In these times of nursing shortages, 50 per cent of the patients thought that they had excellent nursing care; 45 per cent felt that the nursing care was adequate, and only 5 per cent replied that the nursing was inadequate (Fig. 10). While we were of the opinion that the majority of patients were receiving adequate instruction in the hospital, there was a majority request for more instruction in baby care. Some of the patients felt that there was a shortage of nurses at night and on week ends.

In response to the question about acquaintance with the baby at the time the patient left the hospital, 96 per cent replied in the affirmative and 93 per cent of patients felt that the hospital acquaintance with the baby had helped during their first few weeks at home (Figs. 11 and 12). These patient observations are further confirmed by many of the pediatricians who report that they have fewer calls during the first few weeks from mothers who have had their babies under the George Washington University program of mother-infant care.

The most significant criticism centered around inadequacy of toilet and shower facilities, a construction feature which is common to a greater part of the maternity floor. The maternity division was planned before early ambulation became a generally accepted procedure, and in an era of construction when wartime restrictions on building materials were still in effect. As a result there are ample bedpan-sterilizing facilities, but altogether too few toilets. This deficiency is being corrected by additional installations.

The spacing and serving of meals is a problem which was reflected in the returns. A number of patients objected to receiving cold food and many suggested that the evening meal and breakfast were too far apart.

Other hospital procedures about which some patients registered displeasure were as follows: being awakened too early; waiting too long to be admitted; wanting more information for fathers during labor and delivery; requesting that husbands be permitted to stay with them in the labor rooms.

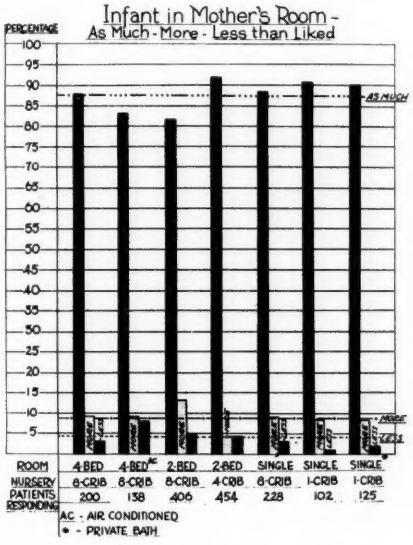


Fig. 8.

Summary and Recommendations

On the basis of professional experiences and patient responses to optional nursery facilities in care of mothers and the newborn certain observations and recommendations can be made.

Maternity services have been removed from homes and centralized in hospitals. Hospitals have become scientifically safe centers for delivery, but antiseptic techniques have overshadowed the science of human relations. Physicians, nurses, and hospital administrators can cooperate to provide all the safeguards of a growing science plus some of those humanities which distinguish a home from a hotel. The majority of mothers who give birth to their infants in hospitals today are healthy. They have healthy infants, and they have highly interested if not completely informed husbands and relatives.

In planning maternity buildings of the future and in the remodeling of current facilities it is hoped that the advantage of an optional nursery arrangement will be apparent. No single type of mother-infant accommodation will be satisfactory to all. In planning multiple choice nursery-room arrangements, the ratio of the various types of accommodations will vary with the hospital, but in general they should be approximately as follows: one-eighth of the accommodations single rooms with nursery and bath; one-eighth single rooms with bath but apart from the nursery; one-half with four-crib nurseries in proximity to double rooms; one-eighth double rooms separate from the nurseries, and one-eighth four-bed rooms adjacent to or apart from the nurseries. Toilet and shower facilities should be provided in a minimal ratio of 1 to every 4 patients.

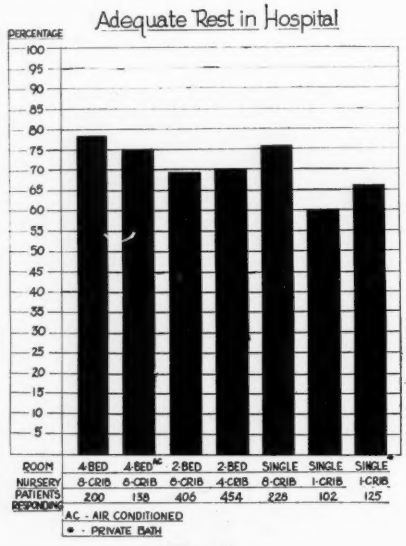


Fig. 9.

Small nurseries should be the centers around which the mothers' rooms are planned. In general, cubicle spaces are unnecessary. Large corridor view windows should permit a ready visualization of all infants at practically all times of the night and day.

Four-crib nurseries have been the most popular of all of the accommodations in the maternity division. During the day they have given a desirable nearness of the infant to the mother and family. At night, with the shades in the mothers' rooms drawn, the nurses care for the infants without disturbance to the mothers. Entrance to the nursery should be from the outer corridor. Nursery noise does not pass through walls nearly as readily as it does through doorways. In planning future four-crib nurseries between double rooms it seems advisable to have small view windows between the nursery and the mothers' rooms approximately 36 inches from the floor with shades which can be controlled from both sides of the wall.

Fig. 13 is an example of an ideal room, nursery, and bath plan prepared by the Public Building Service of the General Services Administration for the proposed District of Columbia Hospital Center, Washington.

With regard to rest in the hospital, it is apparent that there is reasonable room for improvement in current practices. There are so many interrelated components to this problem that no one feature stands out as predominant. In the plan of care provided at the George Washington University Hospital, decentralized nurseries and freedom to have the baby as much or as little as the mother likes have not contributed appreciably to lack of rest.

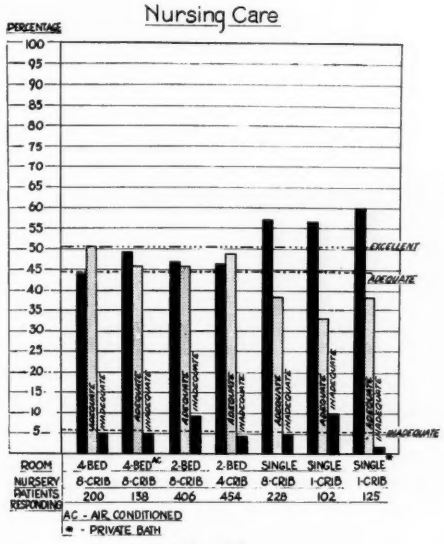


Fig. 10.

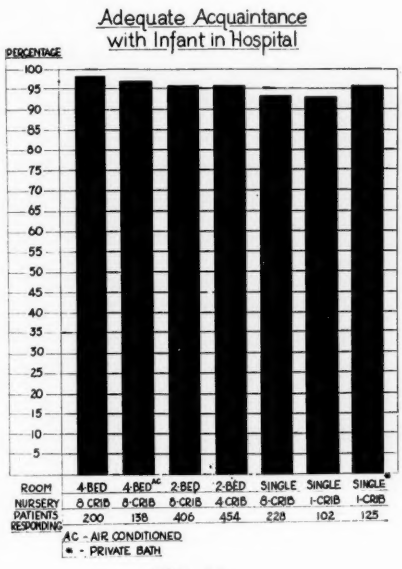


Fig. 11.

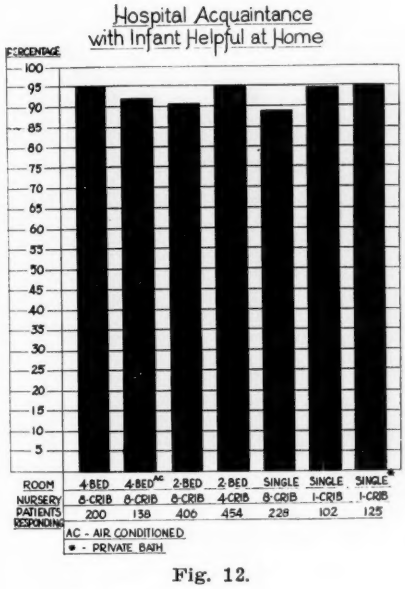


Fig. 12.

Physiologic changes and physical fatigue always follow childbirth. During the immediate puerperal period the mother frequently has a sense of fatigue similar to that which she experienced in early pregnancy. In addition she has

to adjust to new responsibilities. Involuting and temporarily distorted genital structures, functionally hyperactive mammary glands, and a disturbed excretory system may interfere with rest. Hospital surroundings which influence rest include: an unknown roommate possibly with a different attitude toward motherhood; variation in dietary habits; a new and frequently harder, smaller bed in which to sleep; physicians and nurses who drop in and out of the room at all hours of the day and night; an unsolicited self-administered bath and a recorded temperature shortly after daybreak, and visitors, many of whom have very little respect for the energies or emotions of the new mother.

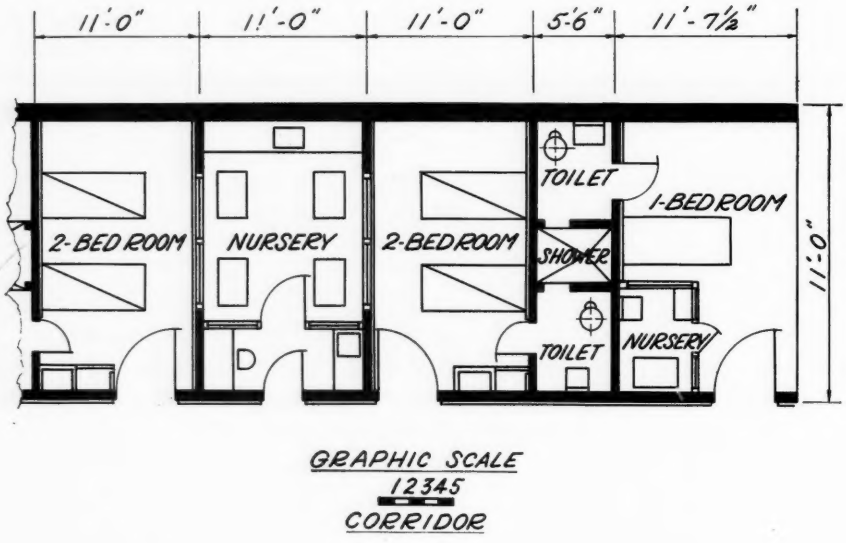


Fig. 13.

To correct some of these disturbing features of maternity hospitalization, it is recommended that patients be allowed to sleep until shortly before breakfast time; that breakfast be served at an early hour followed by mid-morning and late evening nourishment. An afternoon period of rest should be provided in which the patient is not to be disturbed by physicians, visitors, or incoming telephone calls. In the maternity division consideration should be given to the limitation of visitors to one hour during the evening.

In the plan of care presented, nurse-hours need not be increased. More attention must be given to the mother early in the puerperium. As a rule, she will need less instruction after the third or fourth day in the hospital. It has been our uniform impression that no one can care for a newborn baby as well as his own interested and well-informed mother.

Maternity hospitals are natural places for health education. In an informal and healthful atmosphere mothers can enjoy themselves and their infants while they learn from each other and from the staff. The nurse who cares for both mother and infant has an understanding of their relationship to each other. The mother who learns the individual behavior pattern of her own baby, and who learns to supply his needs has a sounder appreciation

and a better understanding of her role as a parent. Mothers and fathers who develop a feeling of adequacy and self-confidence during the period of maternity hospitalization are better prepared for a comfortable life at home with their infant.

Discussion

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—It is a particular pleasure to discuss this paper because of the excellent and well-documented material contained therein, and the personal interest I have had in the subject over a period of years.

Possibly the discussant is so much in agreement with the sentiments expressed that he is unqualified to render an impersonal criticism; however, most of those who hear or read this presentation will agree that three points have been made rather substantially: (1) that the maternity patient appreciates having an intimate contact with her newborn babe; (2) that a new type of hospital architecture is evolving in which accommodations for the mother are centered about small peripheral nurseries; and (3) that excellent records for care of mother and baby can be maintained under this system.

With it all—and again I think that we all agree—the death knell of the large central nursery is being sung.

It is quite proper to recognize the pioneer work which Parks, McLendon, and associates have accomplished in the planning and execution of the maternity floors of the George Washington University Hospital. Those of us who have visited that institution have been impressed by the obvious expenditure of time, effort, and money which has gone into the preparation of the variety of room and nursery accommodations which that institution offers.

The money involved is an important consideration, first, as regards the capital outlay in construction and, second, as to the cost to the patient of room and nursery and individualized nursing service. These must be considerable and someone must foot the bill. In thus approaching the hospital ideal of maternity care the question might be raised whether we are making childbearing, with its considerable fees for hospital, obstetrician, and pediatrician, almost prohibitive to that very class of people who could well be encouraged to have more children.

I dare say that Dr. Parks has turned these thoughts over in his mind many times, and I think that I can recall his saying that, in a number of respects, these architectural arrangements can be simplified and made less costly. That is well to know, for many institutions are interested in developing something of this sort in future hospital construction.

At the Jefferson Hospital we undertook some years ago (July, 1946) a program of closely integrated care of mother and baby, and endeavored to determine whether such a program could be carried out with a minimum of architectural adjustment.

At the meeting of the American Gynecological Society in Williamsburg in May, 1948, we reported preliminary observations on ward and private service. The procedures outlined in that initial paper have been continued, and several studies have subsequently been presented.

Rooming-in of normal full-term babies on a 24 hour basis continues to be mandatory on the ward service. Over 6,000 patients have been handled in this fashion at Jefferson, and 5,000 at the Philadelphia General Hospital. The record is still excellent as regards absence of epidemic infection, high incidence of breast feeding, education of mothers, meticulous care of babies, and the freeing of nurses (who are all too few) for the care of ill patients and premature babies. I do not know how we could bring ourselves to go back to central nursery care in this department of our maternity work.

On the private service, rooming-in has always been on an optional basis for as much of the 24 hours as the patient desires and for as many days of the puerperium as she elects. In most instances the baby is placed with his equipment at the bedside during the day and taken out to a special room of the central nursery at night. Approximately 35 per cent of private patients take advantage of these arrangements. We wish that all might, because of the educational advantages which the plan offers. We feel that more would if small nurseries

were immediately adjacent to their rooms. As a matter of fact, the architecture now under construction envisions on the private floor this plan: a small central nursery, well equipped for the observation and treatment of the newborn in the first 24 hours, and three peripheral nurseries of 6 to 8 cribs each. These three peripheral nurseries are simply arranged and simply equipped and strategically placed among the 2-bed semiprivate rooms.

Our past experience leads us to believe that this arrangement will combine the advantage of central observation at a critical time with the later close association of full-term normal babies and their mothers. Such an arrangement is readily adjustable, reversible if necessary, and not unduly expensive to construct. In the main, it is in close accord with what the essayists have so ably presented this morning.

DR. RALPH REIS, Chicago, Ill.—It is intriguing for those of us who are inclined to be old-fashioned to sit on the sidelines and see this magnificant experiment in rooming-in. However, I cannot help but feel that it is an attempt to swim against the current, and I am reminded of Dr. DeLee's ill-advised tenet that if one cannot be delivered in a maternity hospital, one should be delivered in the home.

If our maternity departments and nurseries are not what they should be, then let us improve them. When Dr. Parks says that the modern nursery is not medically safe, I would question it. When he says it is emotionally unsound, I would be tempted to put that in the category of conjecture. It seems to me that the patients we see in Chicago look forward to a period of isolation and rest, and we are content to concentrate our efforts on making the hospital nursery healthy. We have made no attempts to make it emotionally better than it is because we do not know how to do that.

DR. PARKS (Closing).—I wish to thank Dr. Montgomery for his thoughtful discussion based on wide experience with the care of infants at the mothers' bedside.

For the majority of American women home delivery is a procedure of the past. What we are trying to do, Dr. Reis, is make the hospital a bit more homelike. We do feel that healthier infants have resulted from allowing the mothers to have their babies near by in the hospital. The type of care which can be provided a large number of infants in a single nursery cannot be entirely safe. Disturbed, crying infants fed on a four-hour schedule are a common accompaniment of the large nursery.

This slide (Fig. 13) illustrates the possible pattern for future maternity construction and represents an improvement over the floor plan which we have presented. The important part of this plan is the small nursery. More and more patients are requesting this type of hospital service for the care of their babies.

WHAT ARE THE EARLIEST ENDOMETRIAL CHANGES TO JUSTIFY A DIAGNOSIS OF ENDOMETRIAL CANCER?*

RICHARD W. TE LINDE, M.D., HOWARD W. JONES, M.D., AND GERALD A. GALVIN, M.D., BALTIMORE, MD.

(From the Department of Gynecology, Johns Hopkins University)

THE subject of this paper is not a new one and yet it remains a controversial one. I bring it before you not with the belief that we have found the ultimate solution, but with the knowledge that many of the Fellows of this Society have been interested in the subject for several years and, therefore, it is my hope that this presentation will stimulate discussion by which we may approach a little nearer the true solution.

Through multiple contributions from many clinics and laboratories we have accumulated many valuable data concerning the relation of carcinoma in situ to invasive cervical cancer. As a result, our ideas on that subject have become fairly well crystallized on major points; but no such unanimity of opinion exists concerning the early and suspicious changes in the endometrium in relation to frank carcinoma. The accumulated data to date do not justify an entirely fixed opinion on the part of anyone. The ultimate correct solution to this question is of considerable moment. Not only is it important to the patient to have a correct early diagnosis of endometrial cancer, but from the standpoint of reporting and comparing salvage statistics it is essential that we agree on the microscopic criteria of endometrial malignancy. If one clinic includes as cancer lesions which another clinic considers only suspicious or entirely nonmalignant, there obviously will be therapeutic results which will be entirely misleading when different forms of therapy are evaluated. We must confess that a difference of opinion between pathologists not infrequently exists in our own laboratory and this has stimulated us to study this pathological material intensively.

Serious interest in this subject was first expressed in 1932 when Howard Taylor, Jr., reported his observations on the relationship of endometrial hyperplasia to carcinoma. From a histological and clinical study, Taylor concluded that the histological differentiation of hyperplasia from certain types of carcinoma was difficult and that the possibility of errors in diagnosis was a real one and mistakes might lead to disastrous results. He further concluded that when the hyperplasia is marked the case should be regarded with some suspicion. In 1936 Novak and Yui indicated that there was evidence that there was some sort of relationship between hyperplasia of the endometrium and corporeal cancer. They pointed out that ordinary premenopausal hyperplasia was not only frankly benign histologically but had no relation to

*Presented at the Seventy-sixth Annual Meeting of the American Gynecological Society, Lake Placid, N. Y., June 15 to 17, 1953.

adenocarcinoma. They also called attention to the marked proliferative tendencies of some hyperplasias and particularly to the possible relationship of hyperplasia after the menopause to the development of adenocarcinoma.

In 1947 Gusberg called attention to a pattern of adenomatous hyperplasia of the endometrium which he believed bore a constant relation to estrogen stimulation in both benign and malignant tissue. He also believed that he could observe a graded progression from adenomatous hyperplasia to malignancy. In 1948 Novak and Rutledge called attention to "atypical" endometrial hyperplasias which they considered were often mistaken for carcinoma. They drew their conclusions from two groups of cases. In the first group, atypical hyperplasia was found at curettage. Either without further treatment or with radiological induction of the menopause all patients remained well from one to twenty-one years with one exception. In the second group, curettage was done followed by subsequent hysterectomy without irradiation. No suggestion of carcinoma was found *grossly* on opening the uteri, except in one case, and they concluded that the absence of any *gross* lesion was "almost incompatible with the diagnosis of malignancy."

In 1949 Hertig, Sommers, and Bengloff made an extensive study on the genesis of endometrial cancer. Starting with 500 cases of endometrial cancer there were 67 cases in which the curettings obtained one to twenty-three years before were available for study. For various reasons 35 of these had to be rejected, leaving 32 cases for study. In all of the cases in which the curettings were obtained fifteen to twenty-three years before, the endometrium was normal, but in those cases in which the endometrium was obtained one to thirteen years before, the great majority showed hyperplasia. Hertig and his associates distinguish between "focal hyperplasia" and "adenomatous hyperplasia." They defined "focal hyperplasia" as hyperplasia with infolding of the glandular epithelium and concluded from their studies that it bore no time relation to the development of cancer. They defined "adenomatous hyperplasia" as hyperplasia with outpouching of the budlike, glandular projections into the supporting endometrial stroma. This was the most common lesion found in the group in which the endometrium was available for examination one to thirteen years before the diagnosis of cancer was made. They concluded that "adenomatous hyperplasia" may regress although in many instances it was found to be a precursor of endometrial cancer. They described carcinoma in situ of the endometrium as foci of glands formed of large eosinophilic cells with pale nuclei. The glands were well formed, showed no secretory activity, and nuclear pyknosis and cellular necrobiosis were lacking. If any invasion of either the stroma or myometrium was present, the carcinoma was no longer regarded as in situ. Hertig and co-workers concluded that this microscopic change was not capable of regression and reported six cases of invasive cancer that developed one to eleven years after the diagnosis had been made. Three of these patients died of cancer.

In 1952 Speert published an excellent paper on "The Premalignant Phase of Endometrial Cancer" among 13 cases in which curettings obtained one to

twenty years before were available for study. In only 2 instances were the curettings normal. In the remaining 11 hyperplastic gland patterns were found with infolding papillary projections and/or outpouching of epithelium, crowding of the glands and alteration in staining properties. Speert regarded these hyperplasias as distinct from ordinary functional hyperplasia, as did Novak, and concluded that this type of hyperplasia should be regarded with grave suspicion.

Finally, lest one become overenthusiastic about the existence of proliferative hyperplasia preceding endometrial cancer, attention should be directed to the work of Jones and Brewer who described several cases of endometrial cancer occurring before the menopause in which corpora lutea were demonstrated in the ovaries and the nonmalignant portion of the endometrium showed typical progestational changes. They thus established the fact that in premenopausal women adenocarcinoma may develop within functioning endometrium.

The present presentation is based on a comparison of curettings with the histologic findings in the ultimately removed uterus. The cases are divided into three groups:

Group I is composed of 13 cases in which curettage was done and the interpretations of the curettings were controversial. Because the surgeons in charge believed the curettings to be too suspicious to justify waiting, immediate hysterectomy was done.

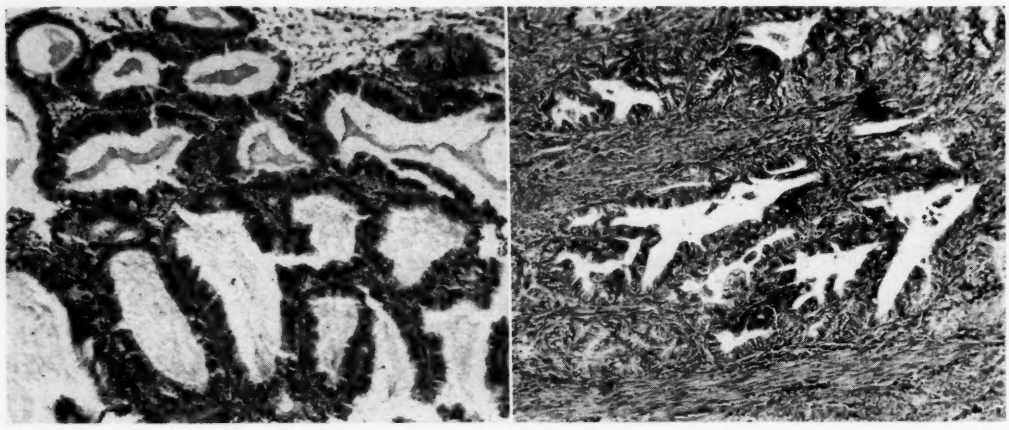
Group II is composed of 14 cases in which curettage was done and the interpretations of the curettings were controversial. Definitive treatment was not carried out immediately. Because of recurrent bleeding, curettage was done ten months to twenty-three years later and frank adenocarcinoma was found.

Group III is a retrospective study of 8 cases of adenocarcinoma of the endometrium in which previous curettings obtained three to thirty-four years before were available for study.

In making a study of this kind several difficulties are encountered. In recent years it has been our custom to give intracavitary radium six weeks before hysterectomy. Hence, in those cases in which the clinician believed he had sufficient histologic evidence to warrant a diagnosis of cancer, radium was applied. This often ruined the endometrium for subsequent histologic study. Therefore, many of the cases for this study have been taken from the remote past so that the unirradiated uterus could be studied.

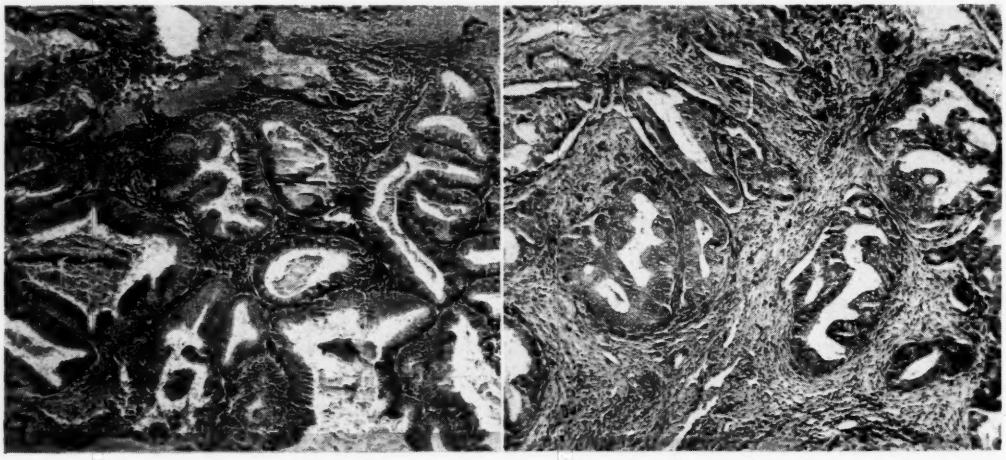
Another difficulty in interpreting the sections histologically arises from the fact that with endometrial adenocarcinoma cytologic changes indicative of malignancy are often not marked, even when the general histologic picture indicates undoubted cancer and even invasion.

A third difficulty arises in evaluating invasion. Even when the myometrium is well invaded, the character of the invading cells is so little altered that it may be difficult to distinguish between adenomyosis and invading adenocarcinoma.



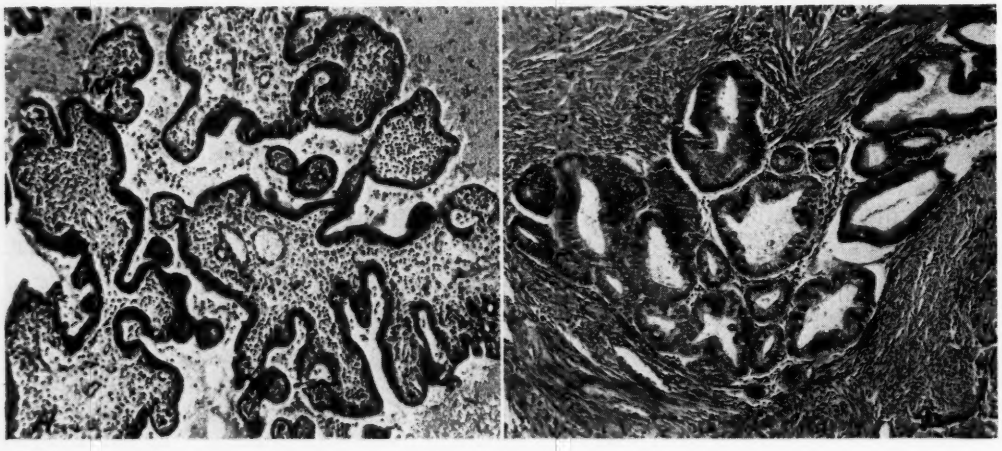
A. *B.*

Fig. 1.—*A*, Curettings, Sept. 27, 1934.
B, Invasive cancer in myometrium, Oct. 1, 1934.



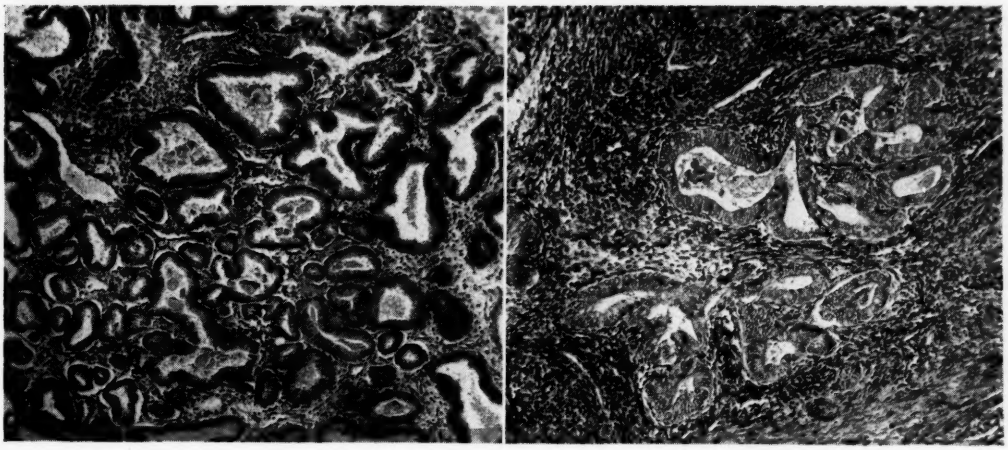
A. *B.*

Fig. 2.—*A*, Curettings, Nov. 21, 1944.
B, Invasive cancer in myometrium, Dec. 7, 1944.



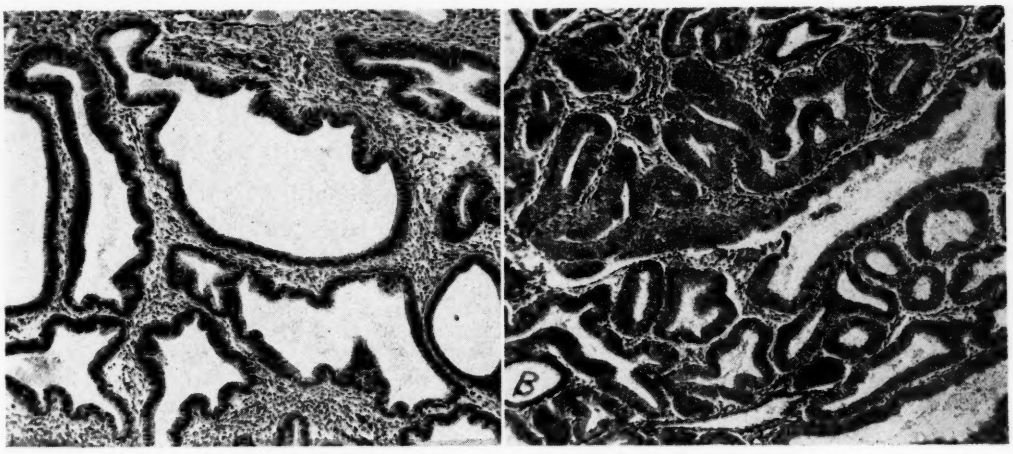
A. *B.*

Fig. 3.—*A*, Curettings, July 9, 1947.
B, Invasive cancer in myometrium, Oct. 29, 1947.



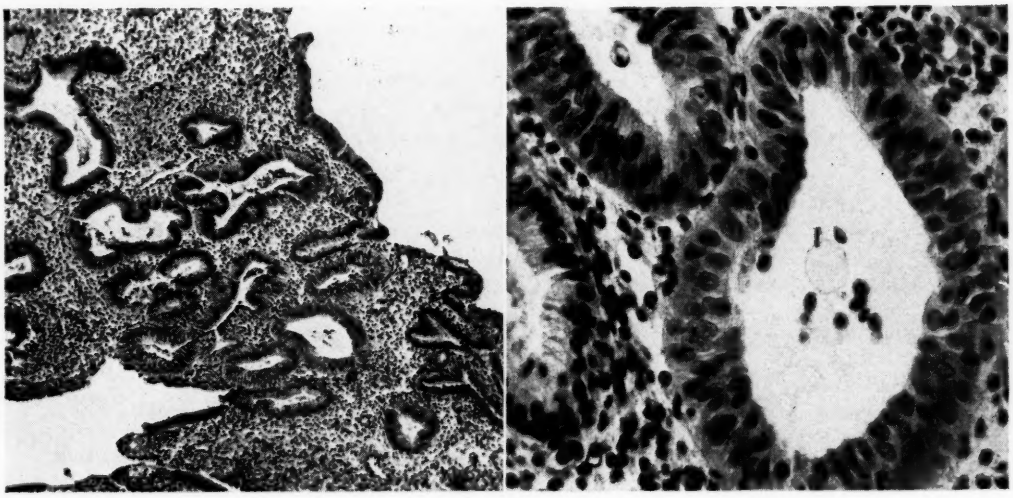
A. *B.*

Fig. 4.—*A*, Curettings, March 14, 1946.
B, Invasive cancer in myometrium, seven weeks later, May 2, 1946.



A. *B.*

Fig. 5.—*A*, Curettings, Nov. 21, 1952.
B, Endometrial picture one month later, Dec. 21, 1952.



A. *B.*

Fig. 6.—*A*, Active endometrium from 53-year-old woman, two and one-half years after irradiation menopause.
B, High-power magnification of one gland, showing pseudostratified active epithelium of gland. Hysterectomy showed undoubted cancer in one area of endometrium.

Nevertheless, recognizing these handicaps, we have attempted to evaluate these cases by thorough histologic examination of the curettings and the subsequently removed uterus.

We shall first present the histological material of the three groups objectively for your consideration and later discuss its possible significance. The first group consists of 13 cases in which there was doubt on the part of some of the pathologists as to the interpretation of the glandular pattern in the curettings. Nevertheless, the clinician in charge believed that the tissue was sufficiently suspicious of malignancy to justify hysterectomy immediately or within a very short time after the curettage. The diagnoses made from the curettings were "atypical hyperplasia," "adenomatous hyperplasia," "proliferative hyperplasia," and by some pathologists, "adenocarcinoma, Grade I." We have the removed uteri for histologic study and for comparison with the original curettings (Table I). Eleven of the 13 cases showed what we interpret as undoubted endometrial cancer. Of these, 5 showed myometrial invasion. Figs. 1 to 4 are representative of this group. In 2 cases the endometrium of the removed uterus might be classified as containing questionable cancer, although in our opinion it is malignant. Fig. 5 is representative of these.

Let us consider now the second group in which there was a lapse of ten months to twenty-three years between the first suspicious curettings and the

TABLE I. GROUP I, 13 CASES
QUESTIONABLE LESIONS FOLLOWED BY IMMEDIATE HYSTERECTOMY

CASE NO.	HISTORY NO.	AGE	POSTMENOPAUSAL	FINDINGS IN UTERUS	REMARKS
27	58376	27	No	Questionable carcinoma No invasion	No radium
33	U. 58215	41	No	Questionable carcinoma No invasion	No radium
34	U. 58086	47	No	Definite carcinoma No invasion	No radium
51	338008	56	Yes	Definite carcinoma Myometrial invasion	No radium
54	345095	60	Yes	Definite carcinoma Myometrial invasion	Radium
56	B.S.	55	Yes	Definite carcinoma ? Invasion	Radium
57	425114	59	Yes	Definite carcinoma Myometrial invasion	No radium
62	427905	53	Yes	Definite carcinoma Myometrial invasion	No radium
63	382069	66	Yes	Definite carcinoma ? Invasion	No radium
65	378910	50	Yes	Definite carcinoma Myometrial invasion	Radium
66	U.M.	45	No	Definite carcinoma No invasion	No radium
75	314224	39	No	Definite carcinoma No invasion	Radium
81	574087	60	Yes	Definite carcinoma No invasion	No radium

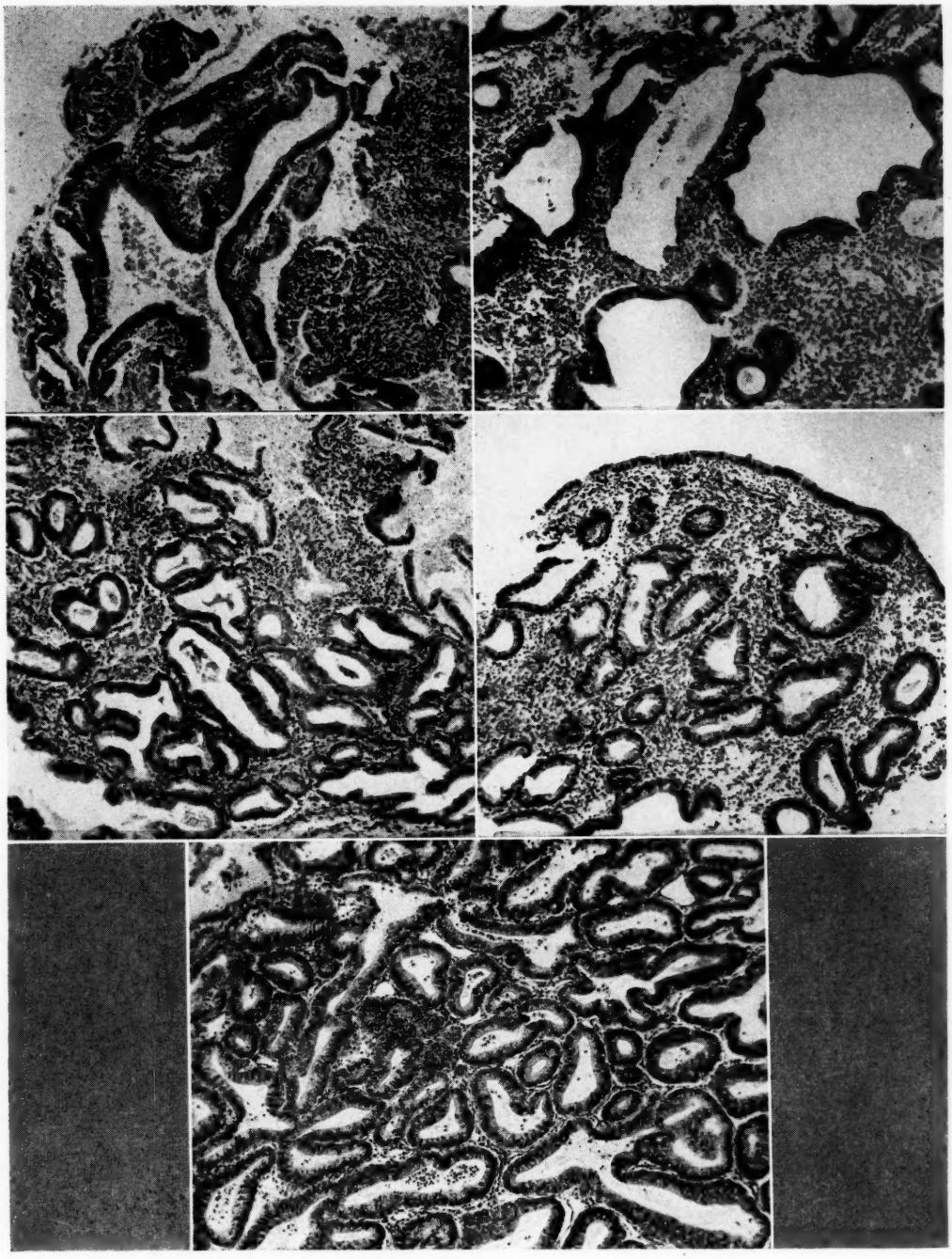


Fig. 7.—Sequential curetting from woman 45 years old at time of first curettage, showing progressively active endometrium and ultimately adenocarcinoma after five years.
A, June 24, 1935.
B, Oct. 4, 1935.
C, Oct. 8, 1937.
D, Oct. 8, 1937.
E, Aug. 30, 1940.

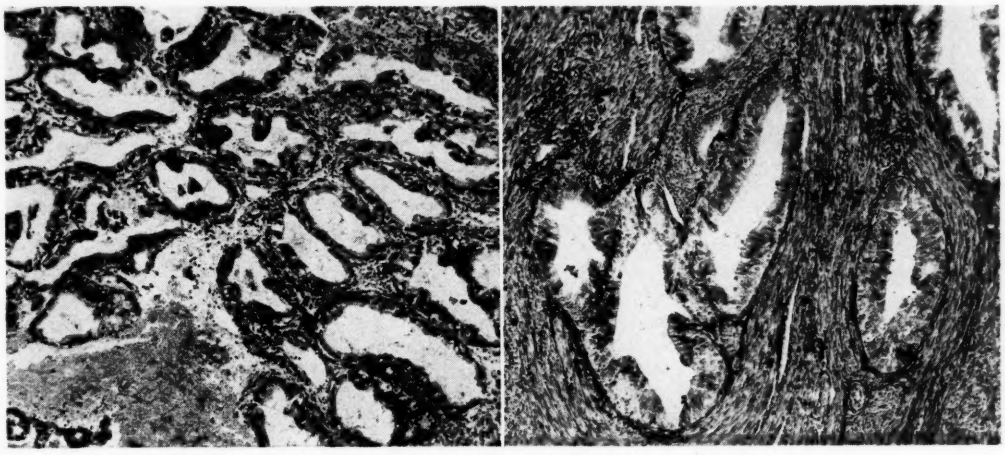
TABLE II. GROUP II, 14 CASES
FIRST CURETTAGE QUESTIONABLE LESION—LAPSE OF 10 MONTHS TO 23 YEARS

CASE NO.	HISTORY NO.	AGE FIRST CURETTAGE	POST-MENOPAUSAL	DATE FIRST CURETTAGE	DATE OF FINAL DIAGNOSIS	FINDINGS IN UTERUS	REMARKS
4	372292	47	No	9/ 6/23	1/ 5/46	Myometrial invasion	No radium
5	389160	38	No	5/24/46	4/11/49	Destroyed by radium	Radium
7	392415	28	No	10/13/33	10/26/35	Myometrial invasion	No radium
9	116838	45	No	6/24/35	8/30/40	Myometrial invasion	Radium
11	165566	44	No	4/ 3/33	3/ 8/39	Myometrial invasion	Treatment irradiation. Died of disease
13	215262	59	Yes	5/26/41	5/15/52	Myometrial invasion	No radium
15	442806	38	No	11/19/31	4/17/51	Myometrial invasion	Radium
16	519112	44	No	1932	10/27/49	Myometrial invasion	Radium
18	St. Jo. Hosp.	58	Yes	5/ 4/48	10/13/51	No invasion	Radium
19	U-13551	32	No	10/ 6/27	4/28/31	No invasion	No radium
23	31133	49	Yes	8/22/24	3/31/26	Myometrial invasion	No radium
24	449768	49	Yes	1/14/48	11/ 9/48	Myometrial invasion	No radium
25	369222	37	No	11/13/45	7/13/50	No invasion	No radium
79	624128	46	No	2/17/51	11/15/52	No invasion	Radium

TABLE III. GROUP III, 8 CASES
CARCINOMA OF ENDOMETRIUM WITHOUT SIGNIFICANT CHANGE IN PREVIOUS CURETTINGS

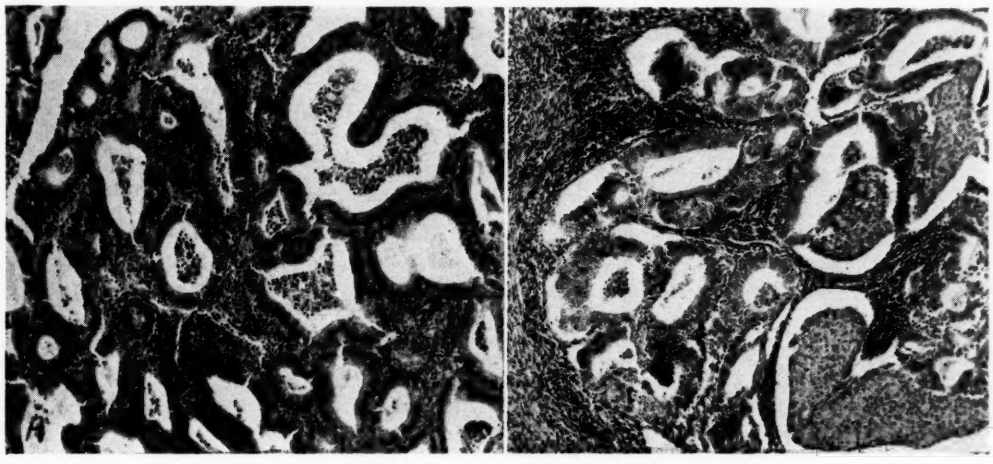
CASE NO.	HISTORY NO.	AGE FIRST CURETTAGE	POST-MENOPAUSAL	DATE FIRST CURETTAGE	PATHOLOGIC FINDINGS	DATE LATER CURETTAGE OR HYSTERECTOMY	PATHOLOGIC FINDINGS	REMARKS
2	399931	34	No	6/26/34	Nonsecretory endometrium	10/16/46 11/13/46	Adenocarcinoma	Died 1/21/47
3	363764	26	No	11/15/31	Postmenstrual endometrium	9/17/46 10/11/46	Adenocarcinoma	Radium
8	190491	26	No	12/15/31	Secretory endometrium	1/13/40 1/16/40	Adenocarcinoma	No radium
14	175244	50	Yes	12/ 2/41	Secretory endometrium	11/ 6/44	Adenocarcinoma	No radium
20	30239	25	No	11/15/25	Cystic hyperplasia	3/12/28 3/15/28	Adenocarcinoma	No radium
21	G. B.	50	Yes	12/22/20	Cystic hyperplasia	12/22/27 12/27/27	Adenocarcinoma	No radium
22	E. S.	49	Yes	6/ 2/16	Premenstrual endometrium	10/ 2/26	Adenocarcinoma	No radium
26	106019	44	No	12/23/25	Cystic hyperplasia	9/ 5/50	Adenocarcinoma	Radium

ultimate diagnoses of malignancy (Table II). The original curettings were variously diagnosed in the terms mentioned above. Study of the curettings or of the uterus which was ultimately removed showed what appeared to us to be undoubted endometrial cancer in all 14 cases. In 9 of the cases cancer was demonstrated invading the myometrium. Figs. 7 to 10 are representative of this group.



A. *B.*

Fig. 8.—*A*, Curettings, Sept. 22, 1924.
B, Invasive cancer in myometrium, two years later, May 31, 1926.



A. *B.*

Fig. 9.—*A*, Curettings, Oct. 18, 1933.
B, Invasive cancer with acanthomatous change, 2 years after curettage, Oct. 26, 1935.

Finally, Group III (Table III) represents a study of earlier curettings from 8 cases of adenocarcinoma of the endometrium. This group simply demonstrates an obvious fact that adenocarcinoma of the endometrium is preceded sometimes by endometrium going through a normal cycle, non-secretory endometrium, or endometrium with glandular cystic hyperplasia.

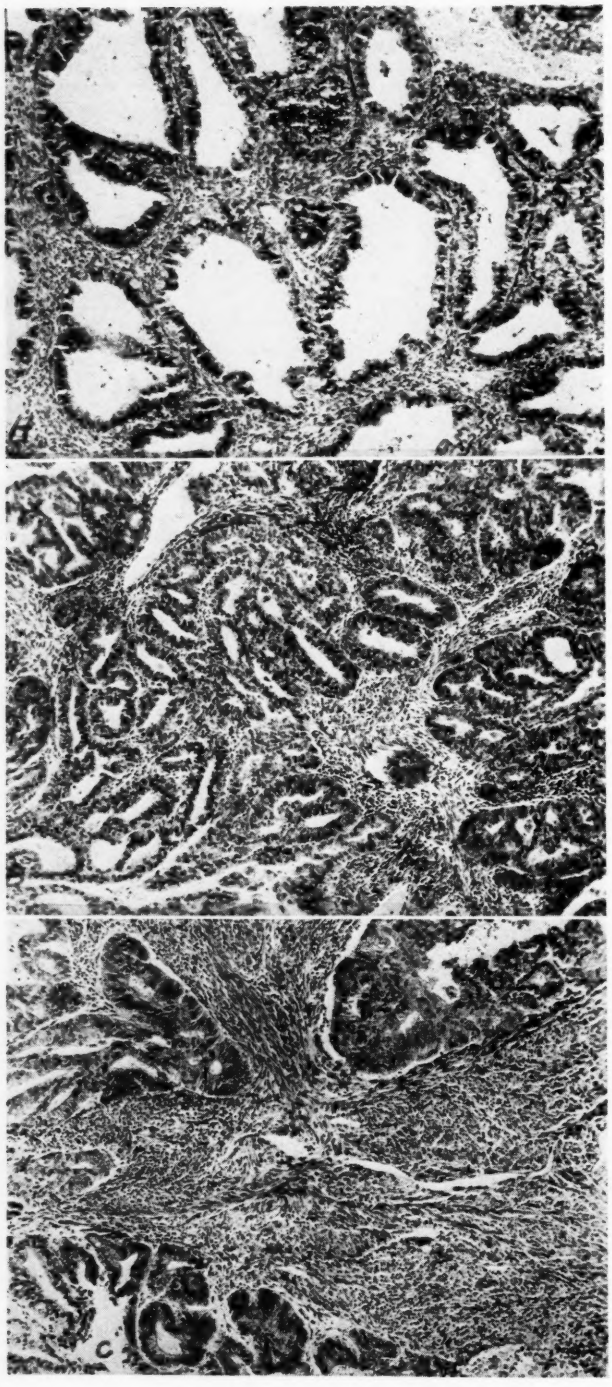


Fig. 10.—*A*, Curettings, Nov. 19, 1931.
B, Curettings twenty years later, Nov. 17, 1951.
C, Invasive cancer found in uterus, slightly over twenty years after first curettage, Jan. 4, 1952.

It may be significant that only 8 such cases were found in our laboratory from three to thirty-four years before the diagnosis of adenocarcinoma in contrast to 27 cases in which the above-described suspicious lesions were found. This corresponds to the experience of Speert who found normal endometrium in only 2 curettings out of 13 cases in which earlier curettings were available for study.

Discussion

What are the characteristics of these questionable endometrial lesions and what do they signify? Hertig and associates have subdivided these lesions into different types which they have designated as "focal hyperplasia," "adenomatous hyperplasia," and "endometrial carcinoma in situ." They characterized focal hyperplasia as a pattern with infolding glandular epithelium. They regarded it as of doubtful importance in the development of cancer. "Adenomatous hyperplasia" was characterized by outpouching of budlike projections into the surrounding stroma. This lesion was found with increasing frequency as the time of development of frank cancer was approached. However, they concluded that the condition might regress. Carcinoma in situ of the endometrium they described as characterized by foci of glands formed of large eosinophilic cells with pale nuclei and abundant cytoplasm. The glands are well formed and show no secretory activity; nuclear pyknosis and cellular necrosis are lacking. There is no stromal invasion. They found this picture one to eleven years before a diagnosis of invasive cancer was made and believed that this condition did not regress. Incidentally, Cullen described this identical picture in his volume, *Cancer of the Uterus,* in 1900 and regarded it as early endometrial cancer.

Although we have not been able to subdivide our histologic material as accurately as Hertig and his co-workers, we have noted all these characteristics of the endometrium preceding frank cancer and are in general agreement with them and with Speert in their conclusions.

It is difficult to do more than point out some of the characteristics of the endometrial changes observed in our material and to attempt to interpret them. In Fig. 1, *A* the glands are large and closely packed, there being very little intervening stroma. The general gland pattern suggests active proliferation and the frequent heavy-staining nuclei suggest nuclear activity. The finding of all gradations of glandular patterns between this and frank cancer together with the finding of muscular invasion in the removed uterus (Fig. 1, *B*) suggests strongly the possibility that the lesion in the curettings is a fact cancer. The same observations might apply to the curettings from a 56-year-old postmenopausal woman shown in Fig. 2, *A*. The finding of such heavy epithelium in the endometrium of a postmenopausal woman can only indicate a response to some stimulation. The uterus removed two weeks later showed invasive cancer and we can only conclude that the original curettings were in fact cancer. The papillary form of epithelial proliferation shown in Fig. 3, *A* has no place in the normal epithelial pattern of a 59-year-old woman. The removed uterus showed invasive cancer (Fig. 3, *B*) and we have concluded that the papillary growth shown in the curettings is part of the malignant growth.

The curetted endometrium shown in Fig. 5, *A* more closely resembles benign premenopausal hyperplasia than any of the former specimens although it appears more proliferative and it was from the uterus of a 53-year-old woman. The age factor we believe to be significant and we view this specimen with grave suspicion of malignancy. The endometrium of the uterus removed one month later (Fig. 5, *B*) has most of its stroma replaced by proliferative glandular tissue, having all the characteristics of cancer including myometrial invasion. The epithelial cells of these glands are light staining, resembling those described by Cullen and Hertig in early endometrial cancer. All gradations between the gland pattern shown in the curettings and that of the final specimen were found and it is difficult not to conclude that the original curettings are an early stage of endometrial cancer.

Another example of the postmenopausal hyperplasia pattern in relation to endometrial cancer is shown in Fig. 6. A 51-year-old woman was given radium for functional bleeding. She ceased menstruating and two and one-half years later again began to bleed. The curettings, showing a hyperplastic pattern, are shown in Fig. 6, *A*. As mentioned earlier in this paper the cytologic changes in the glandular epithelium are often minimal, even when frank cancer exists. Nevertheless, the heavy pseudostratified epithelium lining these glands of the endometrium of a postmenopausal woman we view with concern. Fig. 6, *B* shows this epithelium in high-power magnification. Sections from other portions of this endometrium showed frank cancer.

Considering now the 14 cases in which there was a lapse of ten months to twenty-three years, perhaps something can be learned from a study of sequential curettings. Glancing at the curettings of the 4 cases pictured here, one gets the general impression that although there is evidence of abnormal growth activity, the gland patterns are less suspicious of cancer than the curettings in Group I in which the curetting immediately preceded the hysterectomy.

In Case 9 (Fig. 7) we have the endometrium for study over a period of five years of a woman who was premenopausal at 45, when the first curetting was done. The picture is one of progressive growth activity showing various degrees of a hyperplastic pattern, but with increasingly active-looking epithelium with succeeding years. Finally, the last curettings, five years after the original ones, show definite adenocarcinoma. The uterus removed two months later showed invasive cancer in the myometrium.

Fig. 8, *A* shows a hyperplastic endometrium from a postmenopausal woman of 49 years. A diagnosis of adenocarcinoma is scarcely justified and yet such a picture in a postmenopausal woman suggests some growth stimulus. Less than two years later the myometrium was found to be invaded with endometrial cancer (Fig. 8, *B*).

Fig. 9, *A* shows an endometrium of the adenomatous hyperplastic type. This was taken from a 28-year-old woman and because of her youth the very active-looking glandular pattern was not viewed with as much suspicion as it would have been in a postmenopausal woman, and yet one cannot help being

struck with the fact that this is not ordinary benign glandular cystic hyperplasia. Two years later the woman was found to have invasive adenoacanthomatous cancer (Fig. 9, *B*).

Finally, Fig. 10, *A* is the endometrium from a woman of 38 years. We wish to call attention to the similarity of the gland pattern in this figure to that in Fig. 1, *A*. In the latter case the curettings were from an endometrium in which adenocarcinoma actually existed. In the case shown in Fig. 10, *A* the woman had no sign or symptom of endometrial cancer until twenty years later when another curettage showed adenocarcinoma as shown in Fig. 10, *B*, and hysterectomy done six weeks later showed invasive cancer. Cases such as these two make the problem difficult. The endometrial patterns of the two currettings are almost identical. One appears to be part and parcel of an existing cancer and the other is followed by cancer after twenty years. One cannot escape the thought that perhaps these lesions described as "atypical hyperplasia," "proliferative hyperplasia," and "adenomatous hyperplasia" may bear the same relation to advanced endometrial cancer that carcinoma in situ bears to invasive cervical cancer. It appears that some of these lesions, like epidermoid cancer in situ, may precede actual cancer for many years or may co-exist with it. There is at least the suggestion that the stimulus which ultimately brings about invasive endometrial cancer may in some cases be at work for many years.

Conclusions

From our first group of 13 cases there is the strong suggestion that many lesions that were variously diagnosed as "atypical hyperplasia," "adenomatous hyperplasia," and "proliferative hyperplasia" are in fact carcinoma. This opinion is based upon the frequent finding of these lesions in the same endometrium with advanced carcinoma and the histologic transition of these lesions to the more malignant-appearing ones.

The data presented in our Group II cases suggest that often endometrial carcinoma may be preceded by similar "hyperplastic" lesions for several years.

Our data assembled in Group III indicate that in a smaller group of cases secretory endometrium, nonsecretory endometrium, or glandular cystic hyperplasia may precede the development of cancer up to within three years of the development of frank cancer. Although we have no material to substantiate it, we have no doubt that adenocarcinoma can arise within secretory endometrium as shown by Jones and Brewer.

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Discussion

DR. KARL H. MARTZLOFF, Portland, Ore.—Dr. Te Linde's interesting and critical presentation brings into sharp focus a special and real clinical-pathologic problem as old as the critical histologic study of cancer. It is worth pausing to note the many contributors to this subject who are on the membership roster of this Society (Cullen, Meyer, Taylor, Novak, Hertig, Brewer), and the importance they have attributed to this problem.

While Dr. Te Linde has opened a number of interesting avenues for discussion, I will confine my remarks, because of time limitation, to the single proposition which he has so clearly portrayed in his Group I patients. Here curettings obtained for diagnosis posed the problem of correct interpretation. A vitally practical question is thereby immediately created because, in the absence of satisfactory anatomical evidence, the decision must still be made as to what shall constitute proper therapy. On this depends a patient's ultimate welfare. Consequently, for emphasis, I wish to paraphrase Dr. Te Linde's title: what are the minimal histologic criteria that will promise a reliable diagnosis in cases of atypical endometrial cancer? We are not concerned, therefore, with either the question of noninvasive or intraepithelial carcinoid alterations (cancer in situ), the problem of early cancer, or with cystic endometrial hyperplasia, although conceivably these might come into consideration. But we are confronted, in this controversial group of patients, with the highly important and elementary proposition of being able to diagnose endometrial adenocarcinoma from curettings obtained for biopsy when cancer exists. It is, I believe, axiomatic that diagnostic problems posed by epidermoid cancers are minimal when compared with those that may arise when adenocarcinomas are under consideration. While this is true of cervical adenocarcinomas, as was brought out again by Carter before this Society in 1948, it is particularly pertinent for some forms of endometrial cancer, as has been stressed here by Dr. Te Linde.

The problem under consideration obviously is one that involves critical histologic study. It is apparent then that rapid frozen section studies are not only inadequate but may conceivably sacrifice the piece of tissue which might afford the clue to diagnosis. Therefore, well-prepared, thinly cut, representative, permanent sections are a necessity and can be obtained only by incorporating all of the curettings in one block, as is the custom with Dr. Te Linde's material.

Myometrial invasion in the absence of necrosis is ordinarily not observable in tissue obtained by gentle curettage where cancer is suspected, as in this group of patients. Failure to demonstrate myometrial invasion, therefore, is of no aid in establishing a preoperative diagnosis in a controversial case. However, its demonstration in the removed uterus may be of real help when the endometrial picture itself is still sufficiently unconvincing. Its presence then offers incontestable proof of cancer. It absence, though, does not necessarily rule out the carcinomatous character of either a debatable endometrium or an endometrium that is histologically frankly cancerous. The patients in Group I of Dr. Te Linde's material clearly illustrate this point.

Given a controversial endometrium and no demonstrable microscopic myometrial invasion, what other histologic criteria do we have available for the establishment of a dependable cancer diagnosis? Dr. Te Linde has mentioned them, namely, an abnormal gland pattern and cytologic alterations. One or both of these may be present in sufficient degree to allow a strong but inconclusive suspicion that the endometrium in which they occur represents cancer. We purposely avoid using the term adenoma malignum or mentioning invasion of the interglandular stroma as a diagnostic sign, for in this controversial group stromal invasion, if present, is not recognizable.

Under the foregoing circumstances, one finds oneself in what I consider an unrealistic position. One's interpretative sense then forces one to look for loopholes, such as for example the general extent of a focal, adenomatous, or papillary hyperplasia. If it is localized, and particularly if it is confined to a small area in the zona compactum or spongiosum in a patient under 45 years of age, the urge then is to evade the fundamental

issue and arbitrarily interpret the picture as an atypical benign hyperplasia. Such a disposition is excellent for purposes of cataloguing and for dismissing, if only temporarily, a troublesome problem. It does not answer the question as to whether the debatable lesion is a bona fide cancer. The fact that such a patient may remain well indefinitely after nothing more than a diagnostic curettage still does not prove the lesion noncancerous.

The questions raised today are the same ones that vexed Ruge and Veit, Cullen, von Franqué, and other early students of uterine cancer. On the basis of pure histologic study unaided by other biologic approaches, I doubt our ability to formulate strict diagnostic criteria which will allow us to distinguish unequivocally between a group of so-called typical benign hyperplasias and those atypical adenocarcinomas whose appearance masks their true malignant character.

Finally, the high incidence of correct histologic diagnosis in these controversial endometria and thereby the correct decision as to their management depends upon no single qualification. The greater an individual's critical experience in the correlation of the pathologic and clinical aspects of this problem, the fewer will be his errors. Dr. Te Linde's experience in his Group I patients, therefore, represents an enviable but not unexpected record of competence.

DR. EDMUND R. NOVAK, Baltimore, Md. (by invitation).—The first slide shows the endometrium of a postmenopausal patient who was curetted but had no other treatment. She is alive and well twenty years following curettage.

The second slide represents the curettings from a 72-year-old woman who was admitted because of bleeding of several weeks' duration. Although she denied any therapy for change of life, it was learned later that her family doctor had been administering 1 mg. stilbestrol daily because of postmenopausal osteoporosis. Since the woman was 72 years old and an extremely poor operative risk, we did nothing except discontinue the stilbestrol. She was recuretted 4 months later, and no tissue was obtainable. Curettage has been repeated at yearly intervals, and in the 6 years there has never been any further endometrium obtained.

I believe most of you will agree that both of these lantern slides are compatible with the appearance of the so-called "adenocarcinoma in situ." It might thus seem preferable to think of these atypical proliferative hyperplasias as potentially malignant rather than carcinoma in situ which term suggests irreversibility.

We felt it might be worth while to examine postmenopausal patients with adenomatous endometria more closely and study the ovaries when they were available, excluding cases with a history of estrogen therapy. It was at once apparent that such patients had characteristics similar to those previously associated with fundal adenocarcinoma. Many were obese, hypertensive, or diabetic. There was often a history of a late menopause, infertility, or a previous menstrual irregularity requiring cuettage. Last, the ovaries in these patients with proliferative hyperplasia showed a higher degree of stromal activity (which has previously been noted in conjunction with fundal cancer), and many of these stromal cells appeared identical with theca cells which might be capable of endocrine (estrogen ?) function.

From our studies we infer that proliferative hyperplasia and adenocarcinoma may be variants of some kind of generalized metabolic or endocrine dysfunction with adenocarcinoma an exaggerated and frequent but by no means an inevitable sequel to postmenopausal hyperplasia. The role of estrogen as an inciting factor in such lesions must be regarded as extremely suggestive although unproved.

DR. J. HOFBAUER, Cincinnati, Ohio (by invitation).—The elucidation by only microscopic study of the pathogenetic mechanism involved in the controversial endometrial changes has its limitations. It was twenty years ago that I first embarked on the experimental approach to the problem by the weekly intramuscular implantation of freshly obtained anterior pituitary substance. The meticulous reproduction of both the endometrial

and ovarian structural changes pointed to the incisive part played by anterior pituitary overactivity in endometrial hyperplasia. With the administration of anterior pituitary prolonged for months, the lumen of the uterine glands appeared filled with many layers of proliferated epithelium of the low cuboidal type. In ovariectomized animals the repeated implantation of anterior pituitary substance produced a different pattern. The exuberantly grown basalis with very scanty intervening connective tissue presented an impressive parallel to the diffuse adenoma occurring in advanced age as a blastoma with malignant potentialities. In order to test the influence of both estrogens and gonadotropins on the uterine mucosa, one implantation of pituitary preceded the castration, which eliminated further elaboration of ovarian estrogen and progestin and accounted for the stimulation of the production of gonadotropins by the pituitary basophils, subsequent to the cessation of ovarian activity.

As detailed in a former address, fundal carcinoma may be viewed as the result of a chain reaction in which the disturbed balance of the endocrine mechanism, with the occurrence in the fifth decade of an increase in the number and secretory activity of the basophils and the concomitant elaboration of gonadotropins, occupies a key position. Conditioning the uterine mucosa by arsenic to the induction of neoplasm by hormonal (estrogenic) stimulation determines (AM. J. OBST. & GYNEC., Jan., 1952) the preparation of the hormone-sensitive tissue for the final event when the inhibitory influence of the corpus luteum is in abeyance, while the pituitary basophils act as the trigger mechanism for the premalignant and malignant transformation of the endometrium.

DR. EMIL NOVAK, Baltimore, Md.—This is a subject in which I am very much interested. Dr. Te Linde's work has clearly demonstrated the controversial nature of these lesions, and on this point we are all agreed. As a matter of fact, as he showed his slides, there were several in which my own appraisal would not have agreed with his. There is a certain inevitable borderline group of cases in which no pathologist in the world can state whether or not the irreversible changes have occurred which convert a merely overactive epithelium into epithelium of the killer type characteristic of carcinoma. There are possibilities of error on either side in this unpleasant group of cases. If we are too conservative in the diagnosis of adenocarcinoma, we may give some patients insufficient treatment. On the other hand, if we consider that all these atypical lesions are going to end up as carcinoma, I think we will be making an equally serious mistake.

As a matter of fact, the possible hazard which may come from Dr. Te Linde's excellent paper is that some may get the impression that there is a certain degree of inevitability about these lesions, that they will all end up as endometrial carcinoma. This I do not believe, because we may see these same lesions in youngsters who later menstruate normally, from normal endometria, for many years. I was recently sent a section from a 19-year-old girl which was diagnosed as endometrial carcinoma by the Professor of Pathology of a well-known medical school. The patient was sent to a gynecologist for preoperative radiation and operation, but he was dubious about the case, and repeated the curettage, which showed a perfectly normal endometrium. The previous section had shown a very atypical but benign hyperplasia. I mention this to emphasize that atypical hyperplasia does not necessarily keep recurring.

As for the term endometrial carcinoma in situ, which some have suggested for some of the atypical hyperplasias, I believe that this would be a very ill-advised one. In the endometrium we are dealing with endocrine-induced lesions instead of the more static ones seen in the cervix, such as the so-called carcinoma in situ. The endocrine factors responsible for hyperplasia, either typical or atypical, may be of transient nature, so that finding them in a young woman does not fix her endometrial behavior pattern for life, with perhaps endometrial cancer after the menopause.

There are other objections to applying the term carcinoma in situ to endometrial lesions. The question of invasiveness is a far less important criterion of pathologic malignancy than in the cervix. There are many endometrial lesions which none of us would hesitate to call cancer even though there is no demonstrable evidence of myometrial invasion or even of penetration of the basement membrane. There are still other reasons

why we should not inject this term carcinoma in situ into the field of endometrial pathology, certainly not until we learn a bit more about the real nature and significance of carcinoma in situ in the cervix.

DR. HOWARD JONES, Baltimore, Md. (by invitation).—It was hoped in this study that the gross specimens would be helpful in determining whether each case was one of malignancy or of a less harmful nature. Unfortunately, almost without exception these cases have been subjected to curettage very shortly before the hysterectomy, so that the gross appearance of the specimen was obscured. It has been observed by others that a grossly smooth endometrium is presumptive evidence for malignancy, but perhaps in these early borderline lesions which have not declared their future intention this observation is less helpful.

We have a photograph of a single case operated upon by Dr. Everett in which there was a lapse of time between curettement and hysterectomy. The uterus was removed after a lapse of about one month from the time of the original curetting. There is nothing here that could be considered a gross lesion. There is, however, a remarkable regeneration of the entire uterine cavity for a postmenopausal woman. This is the first case of Group I which showed myometrial invasion. We, therefore, must conclude that in so far as these borderline cases are concerned, the exact nature of the tumor cannot be judged too accurately by the gross appearance at the time of operation.

DR. TE LINDE (Closing).—I had hoped that this presentation would stimulate some discussion and it has. I am not surprised that we have not arrived at the ultimate solution of this question and I doubt whether we ever do get to it. I think there always have been differences of opinion about some of these controversial lesions.

I find it difficult to disagree with anything Dr. Martzloff has said. He has talked about the difficulties in making a diagnosis, which we all too well appreciate, and the more you work with it the more difficulties you encounter.

Dr. Edmund Novak showed two very interesting slides. Even though the first woman has remained well, I think we have to call it an endometrial carcinoma. The woman could have been cured by a good thorough curettage. Such cases have been reported in the literature. As for the second case, I would have no hesitancy in observing such a woman, as Dr. Novak has done, and she has shown no subsequent carcinoma.

Dr. Novak has a third slide which he did not show. It shows a functioning endometrium for a large part of the area and then an area of hyperplasia and arising out of that an endometrial carcinoma. I was very careful to say that the paper of Dr. Brewer and Dr. Jones concerned cases of carcinoma developing within a normal functioning endometrium, which is not quite the same as saying it can develop from a normally functioning endometrium. In this case of Dr. Novak's it would seem that the carcinoma arose from the area of hyperplasia, which did not respond to progesterone as did the rest of it.

Dr. Hofbauer's discussion was interesting, but I cannot help but wonder whether some of the conditions which he ascribes to his implantations might not occur spontaneously. I have seen such lesions in looking at endometria of untreated guinea pigs.

As for Dr. Emil Novak, clinically I do not think we are far apart. He removes some of these controversial uteri just as well as I do, and I believe it is the safe thing to do. I am glad he warned of the possibility of people going overboard on this; there is always that danger. I am sure some of us are responsible indirectly for a great many unnecessary hysterectomies, as careful as we try to be about being sure of the diagnosis before proceeding with definitive treatment. There is a quotation of the late Dr. Holban which several authors have used: "Nicht carcinoma aber besser aus." If it is carcinoma, yes, it is better out, but if it is not carcinoma, it is not better out. Hysterectomy is something that is not to be done lightly, and it is in this controversial group that we have our differences of opinion.

I do believe that in the course of this study I have tended more to the radical side in making a diagnosis of carcinoma than I did before I started the study. When one finds such a high percentage of undoubtedly invasive carcinoma he cannot help being inclined that way.

PREGNANCY ASSOCIATED WITH DISEASES OF THE ADRENAL GLANDS*

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HYPERFUNCTION of the adrenal cortex due to adrenal cortical tumor or hyperplasia resulting in the clinical picture of Cushing's syndrome usually produces amenorrhea, suppression of ovulation, and depression of fertility. Likewise, adrenal cortical insufficiency, although it less commonly produces amenorrhea, greatly suppresses fertility; in fact, as far as could be ascertained,[1, 2] less than 50 pregnancies have been reported in patients with Addison's disease to date. Among women with Addison's disease who did become pregnant the mortality rate has been high in the past. Knowlton, Mudge, and Jailer,[2] commenting on 39 pregnancies in 29 patients with Addison's disease, reported in the literature before 1950, stated that 8 of the 12 patients (67 per cent) whose cases were well documented in this group died during pregnancy, in the immediate puerperium, or soon thereafter.

Even in the absence of pregnancy, hyperfunction and hypofunction of the adrenal cortex may be serious conditions. Plotz, Knowlton, and Ragan[3] reported that 17 of 32 patients (53 per cent) with Cushing's syndrome were dead within an average of five years from the time of the onset of symptoms, the chief causes of death being bacterial infection (46 per cent) and cardiovascular renal complications (40 per cent). Rowntree and Snell,[4] in 1931, stated that patients with Addison's disease who were given the treatment of that day usually survived less than two years. However, with modern substitution therapy for adrenal cortical insufficiency, patients with inadequate adrenal cortical function may be expected to live longer and enjoy greater fertility. Thus, more patients with Addison's disease and postoperative adrenal cortical insufficiency may consult the obstetrician and internist for care during pregnancy.

Hypertension due to pheochromocytoma may be serious in pregnancy. Records of 6 patients with this condition who had 7 pregnancies were gathered from the literature and from their practice by Bowen and associates[5] in 1950. The fetal loss was 4 of the 7; and of the mothers, 2 died of shock post partum and 1 other had convulsions in the sixth month of pregnancy.

Cases Studied

Since there has been little obstetric experience reported in cases of Cushing's syndrome, adrenal medullary hyperfunction due to pheochromocytoma, or adrenal cortical insufficiency, it seemed worth while to study the patients with

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these conditions seen at the Mayo Clinic who had coexisting pregnancies. In this presentation we will discuss the relationship of gestation to dysfunction of the adrenal glands in 11 patients who had 18 pregnancies. These 11 patients were observed at the Mayo Clinic in the years 1940 through 1952. Not all deliveries occurred on the obstetric service of the clinic but satisfactory knowledge of the course of pregnancy, the type of delivery, and the fetal and maternal results was obtained in all the cases reported.

The lesions present and the pregnancies which occurred in the 11 patients whose cases were studied are listed in Tables I and II. Three patients (Cases 1, 2, and 3) had 6 pregnancies while they had active, untreated Cushing's syndrome due to bilateral adrenal cortical hyperplasia; 2 of these patients (Cases 1 and 2) subsequently had 2 pregnancies after the disease had been controlled by the removal of all of one adrenal and three-fourths to four-fifths of the other adrenal gland. In Case 1, postoperative adrenal cortical insufficiency developed, but this did not occur in Case 2. One patient (Case 4) had 1 pregnancy while she had active Cushing's syndrome due to an adrenal cortical tumor. One patient (Case 5) had 2 pregnancies while she had bilateral pheochromocytomas, and 1 pregnancy after adrenal cortical insufficiency developed as a result of the removal of the adrenal tumors. Three patients (Cases 6, 7, and 8) were not pregnant during the course of active Cushing's syndrome, but did have 3 pregnancies after treatment and control of Cushing's syndrome had been accomplished. Of these 3 patients, 2 (Cases 6 and 7) had undergone removal of all of one adrenal and about three-fourths or four-fifths of the other adrenal gland, and 1 patient (Case 8) had had only roentgen therapy to the pituitary. None of these 3 patients presented clinical evidence of adrenal cortical insufficiency, although, in all 3, the urinary excretion of 17-ketosteroids was below normal. In 2 patients (Cases 9 and 10) Addison's disease developed during pregnancy. One patient (Case 11) had 1 pregnancy while under treatment for Addison's disease.

TABLE I. OBSTETRIC RESULTS IN CASES OF ADRENAL HYPERFUNCTION: 5 CASES; 9 PREGNANCIES

CONDITION	PREGNANCY	RESULTS OF PREGNANCIES				
		ABORTION	FETAL DEATH	STILLBORN	NEONATAL DEATH	LIVING AND WELL
Cushing's syndrome.—						
Hyperplasia:						
Case 1	1	1				
	2				1	
	3					1
	4					1
Case 2	1					1
Case 3	1			1		
Cortical tumor:						
Case 4	1					1
Total		1		1	1	4
Pheochromocytoma:						
Case 5	1					1
	2		1			
Total	9	1	1	1	1	5

TABLE II. RESULTS OF PREGNANCY AFTER ADRENAL OPERATION, AFTER ROENTGEN THERAPY OF PITUITARY FOR CUSHING'S SYNDROME, AND IN ADDISON'S DISEASE: 9 PATIENTS

CONDITION OR PREVIOUS TREATMENT	CASE	SPONTANEOUS ABORTION	NORMAL FETAL AND MATERNAL RESULTS
Partial bilateral adrenalectomy for Cushing's syndrome	1*	1	
	2		1
	6		1
	7		1
Roentgen treatment of pituitary for Cushing's syndrome	8		1
Bilateral adrenalectomy for pheochromocytoma	5*		1
Addison's disease	9†		1
	10†		1
	11*‡		1
Total		1	8

*Treated for adrenal cortical insufficiency during pregnancy.
†Postpartum adrenal cortical insufficiency requiring treatment.
‡Cesarean section for abruptio placentae.

Report of Cases*

CASE 1.—After a miscarriage at five months' gestation in England in 1944, the patient, at the age of 28 years, was hospitalized because of fatigue, hypertension, failure of the striae of pregnancy to fade, and truncal obesity. Cushing's syndrome was suspected and exploration of the adrenal glands was advised, but the patient refused operation. Pregnancy occurred again and delivery eventuated at eight months' gestation in December, 1946. The infant died eight hours after delivery. Gain in weight, hypertension, fatigue, and purple striae continued but the menses returned normally, and conception occurred again after three periods. This pregnancy terminated normally at eight months' gestation and resulted in a normal, living female infant. In addition to the signs and symptoms of Cushing's syndrome previously mentioned, exertional dyspnea, amenorrhea, headaches, and a hump in the cervicodorsal region of the back now appeared. A fourth pregnancy terminated at seven months in November, 1948, resulting in the birth of a premature infant that survived. After this delivery, all of the previous symptoms of Cushing's syndrome became worse.

The patient was admitted to the clinic for the first time on July 24, 1950, and was hospitalized immediately. She was found to have widespread purple striae, girdle obesity, a thin skin, a florid, rounded face, "buffalo hump," facial hirsutism, and hypertension. The blood pressure fluctuated between 160 and 180 mm. of mercury systolic and 100 mm. diastolic and the body weight was 180 pounds (81.6 kilograms). Three determinations of the 17-ketosteroids in the urine showed 10.2, 14.5, and 14.8 mg. per twenty-four hours,† and three determinations of corticosteroids in the urine showed 1.16, 2.06, and 1.31 mg. per twenty-four hours.‡

A diagnosis of Cushing's syndrome was made. The condition apparently had been present in at least mild form since before the first pregnancy, more than six years prior to admission to the clinic. On Aug. 5, 1950, about 85 or 90 per cent of the left adrenal gland was removed and on Oct. 17, 1950, total right adrenalectomy was carried out. Moderate hyperplasia of both glands was noted at operation. The patient made a good recovery from the operations, and soon lost the signs and symptoms of Cushing's syndrome. Symptoms of adrenal cortical insufficiency then developed and required treatment with cortisone and desoxycorticosterone acetate.

*The cases in which adrenalectomy was performed were included also in the group reported by Sprague, Kvale, and Priestley.[6]

†The range of normal values for women at the Mayo Clinic for the excretion of 17-ketosteroids in the urine is from 4 to 17 mg. per twenty-four hours.

‡The range of normal values for women at the Mayo Clinic for the excretion of corticosteroids in the urine is from 0.4 to 1.0 mg. per twenty-four hours.

Late in May, 1951, while the patient was taking 12.5 mg. of cortisone by mouth twice a day and 2 mg. of desoxycorticosterone acetate buccally twice a day, she again became pregnant. Because of severe nausea and vomiting, therapeutic abortion was considered at home, but about that time (after two months of pregnancy) spontaneous abortion occurred.

She was seen again at the clinic on three subsequent visits, the last one being in April, 1953. At this time she was in good condition generally. Normal menses were recurring every four to six weeks. The therapeutic regimen on dismissal was 12.5 mg. of cortisone by mouth three times a day and 3 mg. of desoxycorticosterone acetate by subcutaneous injection once a day.

Comment.—This patient had 4 pregnancies while she had active Cushing's syndrome. The pregnancies caused her no special difficulty but none progressed to term. The fetal salvage was 50 per cent. Conception later occurred while she was receiving hormonal replacement therapy for postoperative adrenal cortical insufficiency. Spontaneous abortion ensued.

CASE 2.—This patient, aged 32 years, was admitted to the clinic in November, 1948, complaining of loss of libido, hypertension, excessive gain in weight, and amenorrhea for eight months after the birth of her only child in April, 1947. She had had three scanty periods before her admission. Examination of the patient disclosed roundness of the face, purple abdominal striae, acne, facial hirsutism, edema of ankles, obesity of the trunk, a "buffalo hump," thin skin with a tendency to bruise easily, keratosis pilaris, and muscular weakness. The blood pressure varied between 165 and 180 mm. systolic and 110 diastolic. She weighed 152 pounds (68.9 kilograms). Roentgenograms of the skull and vertebrae showed osteoporosis, and determinations of the amount of 17-ketosteroids and corticosteroids excreted in the urine showed 14.6 and 1.80 mg., respectively, per twenty-four hours.

A diagnosis of Cushing's syndrome was made, and on March 12, 1949, both adrenal glands were explored and found to be about one-third larger than normal size. A specimen was taken from the left adrenal gland and then about 80 per cent of the right was removed. Although the patient was improved by this procedure, active Cushing's syndrome persisted. Consequently, on April 1, 1950, about 75 per cent of the left adrenal gland was removed, following which remission of the disease occurred.

On Nov. 20, 1950, the patient was seen at the clinic complaining of nausea and anorexia, and was found to be in the second month of pregnancy. Save for rather persistent nausea, exhaustion, and backache the pregnancy was normal. Spontaneous delivery of a normal female infant that weighed 7¾ pounds (3.5 kilograms) occurred on July 4, 1951, under the care of Dr. James Shandorf of Minneapolis. The postpartum course was uneventful; menses returned in July and were regular.

The patient was last seen in September, 1951, at which time examination revealed none of the usual clinical findings of Cushing's syndrome. The blood pressure was 126 mm. systolic and 84 mm. diastolic. The value for 17-ketosteroids in the urine was 2.5 mg. and for corticosteroids 0.93 mg. per twenty-four hours. She reported by letter Dec. 26, 1952, that, except for occasional colds, aching, and a tendency to obesity she was in excellent health.

Comment.—Cushing's syndrome developed during this patient's first pregnancy. After bilateral subtotal adrenalectomy had been done, without postoperative development of clinical adrenal cortical insufficiency, she again became pregnant, and progressed fairly normally through this pregnancy, delivery, and puerperium. Thus one delivery occurred during adrenal cortical hyperfunction and one after four-fifths of the adrenal tissue had been removed.

CASE 3.—The patient was a nulligravida, aged 35 years, who was first seen at the clinic Oct. 2, 1944. She had complained of nervousness, tremor, fatigue, and amenorrhea

for the preceding two years. On examination, she was seen to have facial hirsutism, a rounded face, acne, keratosis pilaris, purple striae, ecchymosis, a receding hairline at the temples, truncal obesity, and hypertension with blood pressure of 160 mm. systolic and 120 diastolic. An excretory urogram and roentgenograms of the sella showed nothing significant. The urinary excretion of 17-ketosteroids was 13.0 mg. in twenty-four hours. A diagnosis of Cushing's syndrome was made, and exploration of the adrenal glands was advised but refused.

The patient was next seen nearly six years later on July 5, 1950, in shock from postpartum hemorrhage. She had been delivered of a stillborn fetus eight hours before admission and had a retained placenta. The blood pressure was unobtainable. The relatives gave a history of a difficult forceps delivery. The patient was now 40 years old and this had been her only pregnancy. She was given a transfusion of 1,500 c.c. of whole blood and, after she recovered from shock, the placenta was removed manually and the uterus was packed. The patient was dismissed on the seventh postpartum day. The blood pressure was 128 mm. systolic and 100 diastolic. She weighed 166 pounds (75.3 kilograms).

The patient was seen a third time at the clinic on Sept. 17, 1951, complaining of extreme exhaustion and nervousness. She was found to have advanced Cushing's syndrome and, in addition, congestive heart failure. Examination of the ocular fundi showed narrowing, Grade 1 to 2, and sclerosis of the retinal arterioles with focal constrictions, Grade 2 to 3 (all graded on a basis of 1 to 4), characteristic of hypertensive retinopathy, Group 3. The blood pressure was 210 mm. systolic and 140 diastolic. The urinary excretion of 17-ketosteroids was 6.8 and 7.1 mg. and of corticosteroids 2.71 and 2.43 mg. per twenty-four hours on two occasions.

After treatment of, and improvement in, her cardiac decompensation, about four-fifths of the left adrenal gland was removed. Twelve days later, the entire right adrenal was removed. Although she recovered from these surgical procedures, the severe hypertension continued in spite of medical therapy, and she died on Feb. 13, 1952, less than five months after the adrenal operation, after two cerebrovascular accidents.

Comment.—The disastrous effects of neglect of Cushing's syndrome for nine years are observed in this case. This patient, although undergoing a pregnancy and delivery, postponed treatment so long that the effects of severe hypertension from adrenal cortical hyperfunction eventually led to her death in spite of the removal of all of one adrenal gland and most of the other.

CASE 4.—This patient, aged 31 years, came to the clinic Sept. 25, 1950, stating that in the fourth month of pregnancy her blood pressure had become elevated and she had noted facial hirsutism, acne, edema of the feet, and purplish striae of the legs and thighs. During pregnancy her weight had increased from 140 to 165 pounds (63.5 to 74.8 kilograms) and she had been hospitalized twice for treatment of edema. In April, 1949, she had gone into labor spontaneously at thirty-four weeks and had been delivered of a normal infant that weighed 7 pounds, 6 ounces (3.4 kilograms). Amenorrhea had persisted since that time and the patient had noted no engorgement of the breast as she had after her other 2 deliveries.

The pertinent physical findings were a florid face, muscular weakness, purple striae of the legs, facial hirsutism, acne, a "buffalo hump," thin skin, keratosis pilaris, and a blood pressure of 170 mm. systolic and 110 diastolic. Urine collected for twenty-four hours showed the presence of 2.7 mg. of 17-ketosteroids and 2.08 mg. of corticosteroids. At operation on Oct. 7, 1950, the left adrenal gland was found to be atrophic and the right adrenal was found to contain an adrenal cortical carcinoma, Grade 1, measuring 4 by 3 by 2.5 cm., with atrophic adjacent adrenal tissue. The entire right adrenal was removed. Following this procedure the patient's Cushing's syndrome disappeared and she has remained well. Her menses returned about ten weeks after operation.

Comment.—A normal delivery occurred while this patient had Cushing's syndrome due to hyperfunctioning malignant adrenal cortical tumor. The en-

tire right adrenal gland was removed along with the tumor. By now she presumably has one normally functioning adrenal and should present no medical or obstetric problem if she becomes pregnant again.

CASE 5.—The patient, aged 28 years, was 1 of 3 siblings, all of whom were found at operation to have large bilateral pheochromocytomas producing severe hypertension. She was first seen at the clinic in August, 1951, at which time she had been married nine years. In 1942, she had experienced headaches and momentary attacks of syncope, but these ceased within six months. In the third trimester of her first pregnancy, in 1946, hypertension developed, with slight albuminuria; attacks of dyspnea, palpitation, pallor, and severe occipital headaches also began. When nervous or upset, she complained of substernal pain and tachycardia. The delivery was normal at term and a living infant was born. Postpartum systolic blood pressure had varied between 172 and 212 mm. The attacks described above continued post partum at intervals of one hour to two days. A second pregnancy in 1948 resulted in a fetal death in utero at six months' gestation with spontaneous delivery one month thereafter. The blood pressure became higher post partum and the patient began to suffer from a constant headache and intolerance to heat.

At the time she was admitted to the clinic on Aug. 11, 1951, the blood pressure was found to be 190 mm. systolic and 130 diastolic, the pulse rate 108, and the weight 100 pounds (45.4 kilograms). An excretory urogram was negative. Examination of the ocular fundi revealed retinal arteriolar narrowing, Grade 1+, focal constrictions, Grade 1+, and hypertensive sclerosis, Grade 1 to 2. Two small cotton-wool patches were seen in each fundus. The basal metabolic rate was +48 per cent. Tests for pheochromocytoma using histamine, phentolamine (Regitine) and piperoxan hydrochloride were all positive.

Abdominal exploration was carried out on Aug. 23, 1951, with precautions for regulating the blood pressure throughout the operation. Bilateral pheochromocytomas were found and removed. No adrenal tissue could be seen in either operative site at the conclusion of the operation. The patient made a satisfactory convalescence, with the blood pressure stabilizing at a normal level (130 mm. systolic and 90 diastolic). The patient was dismissed from the hospital on September 2, but because of the likelihood that adrenal cortical insufficiency would develop, she was kept under close observation.

On September 9, the patient was readmitted to the hospital because of adrenal cortical insufficiency. She was weak and drowsy, complained of epigastric pain and anorexia, and had a temperature of 101° F. The water test was done and was positive in both parts; 25 mg. of corticotropin administered subcutaneously caused no decrease in the eosinophil count in the peripheral blood four hours later, and the intravenous infusion of 20 mg. of corticotropin over an eight-hour period each day for three consecutive days caused no increase in the low level of 17-ketosteroids in the urine (0.6 to 0.8 mg. per twenty-four hours). Treatment was instituted for adrenal cortical insufficiency, and, on September 29, the patient was dismissed from the hospital with instructions to use the following therapeutic regimen: 6.25 mg. of cortisone by mouth four times a day; 2 mg. of desoxycorticosterone acetate (buccal) twice a day, and 5.0 Gm. of extra salt a day. The patient had not menstruated since immediately before her operation in August, but apparently conception occurred at her first postoperative ovulation on about November 1, because signs of pregnancy developed and she felt life on February 1.

The patient's pregnancy progressed satisfactorily under the prenatal care of Dr. J. B. Roth of Morris, Illinois. She returned to the clinic June 24, 1952, in the eighth month of her pregnancy for the rest of her prenatal care and delivery. Treatment at home had been carried on without change except that the dose of cortisone had been reduced about March 1 to 6.25 mg. twice a day. At the time of admission to the clinic, the dose of cortisone was increased to 12.5 mg. three times a day but decreased four days later to 12.5 mg. twice a day because of edema of the ankles. The values for serum urea, potassium, sodium, chloride, and carbon dioxide combining power were normal. The remainder of the prenatal period was also normal; the blood pressure on seven readings

varied from 112 to 130 mm. systolic and 68 to 84 mm. diastolic. No albuminuria was observed and the patient felt well. Results of the twenty-four-hour urinary excretion of 17-ketosteroids and corticosteroids are given in Table III.

TABLE III. POSTADRENALECTOMY ASSAYS OF URINARY EXCRETION OF 17-KETOSTEROIDS AND CORTICOSTEROIDS IN RELATION TO PREGNANCY

DATE	MG. PER 24 HR. 17-KETOSTEROIDS*	MG. PER 24 HR. CORTICOSTEROIDS	HORMONE TREATMENT
Case 5†			
Sept., 1951			
10-11	0.7	0.34	None
15-16	0.7	0.39	Corticotropin—25 mg. t.i.d. (intramuscularly)
16-17	0.8	0.99	Corticotropin—25 mg. t.i.d. (intramuscularly)
17-18	0.6	0.60	Corticotropin—20 mg. (intravenously)
18-19	0.7	0.72	Corticotropin—20 mg. (intravenously)
19-20	0.6	0.49	Corticotropin—20 mg. (intravenously)
20-21	0.6	0.47	None
Average when receiving corticotropin or no treatment	0.7	0.57	
Sept., 1951 23-24	1.6	0.72	Cortisone—6.25 mg. t.i.d. by mouth
June 25-26, 1952, 8 mo. gestation	4.9	1.11	Cortisone—6.25 mg. t.i.d. by mouth
July 23-24, 1952, 4 days post partum	2.1	1.57	Cortisone—6.25 mg. b.i.d. by mouth
Case 7‡			
Oct., 1948	0.5	0.42	
Nov., 1948		0.34	None
April, 1949	3.1	0.40	
Average	1.8	0.39	
Nov., 1951, 6 mo. gestation	6.3	1.06	None

*Mg. per 24 hour volume of urine.

†Adrenal cortical insufficiency after surgery for bilateral pheochromocytoma.

‡Partial bilateral adrenalectomy for Cushing's syndrome, with no subsequent adrenal cortical insufficiency.

Labor began spontaneously on July 19, 1952, and when the patient was admitted to the obstetric service at 1:30 A.M. the contractions were coming every ten minutes. At this time 200 mg. of cortisone was administered intramuscularly. Within an hour after admission, the contractions were recurring every three to four minutes and lasting forty to fifty seconds. Analgesia throughout labor consisted of 3 grains (0.2 Gm.) of secobarbital (Seconal) and 75 mg. of meperidine hydrochloride (Demerol). By 4 A.M., a cervical dilatation of 5 to 6 cm. had been attained and the patient was therefore moved to the delivery room, but secondary inertia developed with the contractions becoming entirely ineffective. After complete lack of progress for forty-five minutes, an intravenous drip of oxytocin (Pitocin 1:10,000) was carefully administered and effective contractions and dilatation of the cervix returned. At vaginal examination, the cervix was found to be dilated 8 to 9 cm. and soft with the station +3. Soon after the administration of oxytocin was started, a blood pressure of 200 mm. systolic and 100 diastolic was recorded. This sudden appearance of hypertension was attributed to the intravenously administered oxytocin, as pointed out by Jackson and Decker.[7] Since considerable apprehension and restlessness were observed also, delivery was easily and quickly effected by pushing the cer-

vix over the fetal head and rotating the occiput with forceps by the key-and-lock technique from left posterior to left anterior presentation. Easy low-forceps extraction of a normal, living female infant that weighed 2,850 grams was accomplished after a routine left mediolateral episiotomy had been done. Inspection of the cervix showed it to be intact. Anesthesia for the delivery consisted of pudendal block and local infiltration by 1 per cent solution of procaine supplemented by small amounts of nitrous oxide and ethylene. Both cortisone and a 1:10,000 solution of l-Arterenol (norepinephrine) were available for intravenous administration had acute adrenal insufficiency appeared but they were not required.

During the puerperium the breast milk was analyzed by Dr. H. L. Mason, who reported that an alcoholic extract of the milk subjected to chromatographic purification showed 0.71 mg. of steroid substances per 100 c.c. calculated for cortisone. He pointed out, however, that this procedure does not guarantee that all of the formaldehydogenic material is steroid in nature. This value should be considered as the upper limit of the amount of cortisone and not be considered an accurate value for the amount of cortisone actually present.

The placenta was extracted in the laboratory of Dr. A. Albert for corticotropin and tested on rats with negative results up to 5 Gm. equivalents of the extract. Assay of the maternal blood for corticotropin gave negative results and assay of the fetal blood gave a borderline result (21 mg. per cent fall in adrenal ascorbic acid in rats, 25 mg. per cent being considered a positive result).

The patient wrote on December 18, 1952, stating she and the baby were in excellent health.

Comment.—This patient had 2 pregnancies while she had bilateral pheochromocytomas; 1 pregnancy terminated in a normal baby and 1 ended in spontaneous abortion. At operation the pheochromocytomas were removed, along with almost all (if not all) of both adrenal glands. After operation, adrenal cortical insufficiency developed which responded well to treatment with cortisone by mouth, desoxycorticosterone acetate given buccally, and extra salt. Conception occurred at the first ovulatory opportunity after the development of adrenal cortical insufficiency. The pregnancy progressed satisfactorily and delivery was accomplished without undue difficulty. To our knowledge, this is the first patient to progress through a normal pregnancy and delivery after bilateral adrenalectomy.

CASE 6.—This patient, aged 36 years, came to the clinic in February, 1949, complaining of weakness, a gain from 175 to 221 pounds (79.4 to 100.2 kilograms), headaches, hypertension, loss of libido, and amenorrhea of two months' duration. Physical findings included a blood pressure of 154 mm. systolic and 120 diastolic, truncal obesity, florid and rounded face, acne, thin skin, purple striae, a "buffalo hump," facial hirsutism and keratosis pilaris. Urinary excretion of 17-ketosteroids at this time was 17.6 mg. and of corticosteroids 1.95 mg. per twenty-four hours.

A diagnosis of Cushing's syndrome was made and on Feb. 22, 1949, the adrenal glands were explored and found to be normal in size. An estimated three-fourths of the left adrenal was removed. At a later date (Oct. 13, 1949) total right adrenalectomy was performed and a complete remission of Cushing's syndrome followed.

The patient became pregnant in the late spring of 1952 and progressed normally through her pregnancy to delivery of a living male infant on Feb. 28, 1953. Dr. I. Vandermyde of Morrison, Illinois, gave her obstetric and medical care throughout this pregnancy. The puerperium also was normal.

Comment.—This patient evidenced no adrenal cortical insufficiency at any time after subtotal adrenalectomy and went through pregnancy, delivery, and the puerperium uneventfully without supportive therapy.

CASE 7.—This patient, aged 36 years, was admitted to the clinic March 30, 1948, complaining of weakness, excessive gain in weight, and loss of libido for three or four months. Menses were normal. She had had 8 normal pregnancies. On examination purple striae, thin skin, acne, and blood pressure varying between 158 and 210 mm. systolic and 108 and 112 diastolic were noted. The 17-ketosteroids and corticosteroids in the urine were 13.8 and 2.18 mg. per twenty-four hours, respectively. A diagnosis of Cushing's syndrome was made but since the disease was in an early stage operation was not urged at that time.

The patient returned in May, 1948. Since the disease had progressed considerably in the preceding six weeks, operation was advised. On May 14, about two-thirds of the right adrenal gland was removed. At a later date (Oct. 8, 1948) total right adrenalectomy was carried out. Following this procedure the Cushing's syndrome went into a complete remission.

In October, 1951, she became pregnant and progressed uneventfully through the pregnancy without evidence of adrenal cortical insufficiency and without trouble except for some weakness and intermittent nausea and vomiting. Spontaneous delivery of a normal female infant that weighed 8 pounds, 9 ounces (3.9 kilograms) occurred on July 7, 1952. She had no difficulty post partum and has remained well. She was cared for during her pregnancy and delivery by Dr. Malvin I. Hauge of Clarkfield, Minn. The results of the determinations of 17-ketosteroids and corticosteroids in the urine are given in Table III.

CASE 8.—This patient, aged 18 years, was admitted to the clinic on June 25, 1940. She had been in good health until August, 1939, when rather severe headaches began to occur two or three times a week. Since then her weight had increased from 127 to 140 pounds (57.6 to 63.5 kilograms). In February, 1940, hirsutism of the face, legs, shoulders, breasts, and abdomen was noted, and amenorrhea began. In March, the systolic blood pressure was 160 mm. and acne developed.

On examination, the patient presented the typical features of Cushing's syndrome. Blood pressure varied between 128 and 150 mm. systolic and 82 and 104 diastolic. She excreted 3.4 mg. of 17-ketosteroids in the urine per twenty-four hours. The adrenal glands were explored on July 4, 1940, and appeared normal. Courses of roentgen therapy were administered to the pituitary on six occasions, July, September, and December, 1940, August, 1941, October, 1944, and January, 1945. After the first course of roentgen therapy menses began again and continued normally, except for an occasional skipping of a period, until June, 1941.

The patient was seen again at the clinic on Aug. 11, 1941, at which time she weighed 134 pounds (60.8 kilograms), and the blood pressure was 128 mm. systolic and 74 diastolic. The hirsutism had increased, but except for frequent headaches she felt well. At this time she was found to be pregnant. Pregnancy progressed normally and a normal female infant was delivered uneventfully on March 3, 1942.

The patient was seen at the clinic on four subsequent visits, the last one being in June, 1946. Each time she had features of Cushing's syndrome in partial remission.

The patient died on Dec. 24, 1950.

CASE 9.—This patient, gravida i, para 0, aged 19 years, had always been in good health until she became pregnant. Her last menstrual period before the pregnancy had been in April, 1949. Early in the pregnancy she had experienced mild hyperemesis, but not enough to require parenteral administration of fluids. Blood pressure ranged from 90 to 100 mm. systolic and 60 to 65 diastolic, and was usually nearer the lower figure. Edema appeared at the thirty-seventh week of the pregnancy but was fairly well controlled by a diet low in salt and the use of Salyrgan. Prenatal care had been given by her home physician, Dr. Paul C. Leck of Austin, Minn., who delivered her of a normal infant weighing 7 pounds, 6 ounces (3.4 kilograms) by episiotomy and low forceps on Jan. 2, 1950. Her postpartum course in the hospital and for two days at home was uneventful

but on the eighth postpartum day, after taking a saline cathartic, she became weak, began to vomit, and went into shock. When she was seen at home, the blood pressure was 90 mm. systolic and 60 diastolic, and by the time she had arrived at the hospital, it could not be obtained. The respiratory rate was rapid, and the pulse was weak and fast. The patient was conscious but too weak to talk and appeared to be in extremis. A dusky hue was noted on the skin and some dark freckles were observed. Dr. Leck made a presumptive diagnosis of adrenal crisis and promptly administered intravenously aqueous adrenal cortical extract and a solution of saline and glucose. The response was excellent; the blood pressure soon rose to 108 mm. systolic and 72 diastolic, and the patient improved dramatically.

The patient was admitted to the clinic nine days post partum on Jan. 10, 1950. Increased pigmentation of the skin, one pigmented patch on the oral mucosa, hypotension, weakness, nausea and vomiting were found. The value for blood urea was 78 mg. per 100 c.c. The urinary excretion of 17-ketosteroids was 1.2 mg. per twenty-four hours. Twenty-five mg. of corticotropin administered subcutaneously caused no significant decrease in the eosinophil count in the peripheral blood four hours later.

A diagnosis of Addison's disease was made. On treatment with 3 Gm. of extra salt in her diet and 3 mg. of desoxycorticosterone acetate (cortate) buccally each day her symptoms of adrenal cortical insufficiency improved. She has remained well since.

Comment.—This case illustrates that in rare instances serious postpartum collapse may be the first conclusive evidence of Addison's disease. The weakness, nausea, vomiting, and increased pigmentation occurring during pregnancy in such patients could be due either to Addison's disease or to pregnancy.

CASE 10.—This patient, aged 21 years, had a normal pregnancy and delivery elsewhere in July, 1947. She had vomited intermittently throughout the pregnancy and her weight had decreased from 176 to 156 pounds (79.8 to 70.8 kilograms). Labor had been induced near term with normal delivery of a living infant on July 22, 1947. On the fourth postpartum day tubal ligation had been done by the abdominal route. Following this the patient did not feel as well as usual, but left the hospital on August 12. She returned to the hospital August 20 complaining of extreme weakness, lightheadedness, palpitation, and tachycardia. During the preceding three weeks freckles had become pronounced on the skin, and pigmentation had increased in spite of the fact that she was in the puerperium. No oral pigmentation was noted. When the patient left the hospital on Sept. 1, 1947, she weighed 145 pounds (65.8 kilograms) and was continuing to have occasional attacks of vomiting.

She was hospitalized again in November, 1947, at which time a diagnosis of Addison's disease was made, which was treated with extra salt in the diet and the subcutaneous injection of 1.5 c.c. of desoxycorticosterone acetate daily. However, she continued to have symptoms of adrenal cortical insufficiency.

The patient was admitted to the clinic April 18, 1948, having lost 37 pounds (16.8 kilograms). The twenty-four-hour urinary excretion of 17-ketosteroids was 0.3 mg. and lymphocytosis with a cell count ranging from 48 to 56 per cent was observed. Treatment consisted of the daily subcutaneous injection of 2 mg. of desoxycorticosterone acetate and the addition of 4 Gm. of extra salt to her diet. She was dismissed from the clinic in good condition on May 7, 1948.

Comment.—This patient was another in whom Addison's disease became evident post partum, although not by a crisis immediately after delivery.

CASE 11.—This patient, aged 20 years, was first seen at the clinic Aug. 2, 1951, for treatment of Addison's disease. During the middle of her senior year in college, within a period of a month, she noted the rapid onset of exhaustion and inability to concentrate, and her scholastic record, which had previously been very high, declined. During this

time freckles appeared on the face and lips and her summer tan persisted into the winter. A diagnosis of Addison's disease was made elsewhere and treatment with 2 mg. desoxycorticosterone acetate buccally per day was begun.

On admission to the clinic a blood pressure of 102 mm. systolic and 70 diastolic and pigmentation of the skin, especially in the region of the axillary folds, were noted. There was no decrease in the number of eosinophils in the peripheral blood four hours after the injection of 25 mg. of corticotropin. The urinary excretion of 17-ketosteroids was 0 and that of corticosteroids 0.49 mg. in twenty-four hours. The first portion of the water test was positive but the second was negative. The Cutler-Power-Wilder test was positive. Treatment with 5 mg. of cortisone taken orally twice daily, 2 mg. of desoxycorticosterone acetate taken buccally twice daily, and 5 Gm. of extra salt each day was begun. The patient did well on this program and was dismissed on Aug. 18, 1951.

The patient was married soon thereafter and shortly became pregnant. She continued the therapeutic program and her pregnancy progressed uneventfully until she went into labor near term, at which time she showed definite evidence of abruptio placentae, with fetal distress. Because of this, it was decided to do a cesarean section. Four hours before the operation she was given 100 mg. of cortisone intramuscularly and 25 mg. orally. A normal baby was delivered at 2:30 A.M., January 16, by cesarean section. From 12:01 A.M. to 12 P.M. of the day of the cesarean section, the patient received 200 mg. of cortisone intramuscularly in divided doses. The following day one injection of 50 mg. of cortisone was given intramuscularly, after which she then began to take 5 mg. of cortisone by mouth four times a day. Aside from a rise in blood pressure to 190 mm. systolic and 100 diastolic on the fifth postpartum day, the postoperative course was uneventful. Except for some feeding difficulty, the infant's progress was normal. Drs. T. J. Luellen and R. A. West, of Wichita, Kan., supervised the medical and obstetric care, respectively, during pregnancy.

Pregnancy Associated With Hyperfunction of Adrenal Cortex: Cushing's Syndrome

It has frequently been emphasized that women with Cushing's syndrome are infertile. However, as this study illustrates, this is not absolute, and some women with this disease do remain fertile. Seven pregnancies occurred in 4 women with active, untreated Cushing's syndrome in our series (Table I). The results of these 7 pregnancies were as follows: 1 spontaneous abortion; 1 unexplained neonatal death; 1 stillbirth from dystocia; and 4 normal, living infants.

Varying degrees of hypertension were present in all cases but no mention of albuminuria of more than Grade 1 (on a grading basis of 1 to 4) or other evidence of superimposed pre-eclampsia could be found in the records or in communications from the physicians giving obstetric care.

It seems, then, that the chief threat to pregnancy from adrenal cortical hyperfunction is chronic hypertension. The fetal mortality rate in this small group of patients with Cushing's syndrome was 3 of 7 (43 per cent), although 1 fetal death resulted from severe dystocia. All mothers survived deliveries without immediate untoward effects, although 1 patient (Case 3) who suffered a severe postpartum hemorrhage and recovered on proper therapy died twenty months later from a cerebral accident. She had refused treatment of Cushing's syndrome for seven and one-half years. Another patient died eight years post partum and eleven years after the onset of Cushing's syndrome. The average survival of all patients from the onset of adrenal cortical hyperfunction until death or the present date is slightly more than seven years.

Pregnancy Associated With Hyperfunction of Adrenal Medulla: Pheochromocytoma

To the records of 6 patients with pheochromocytomas who had 7 pregnancies which Bowen and associates[5] gathered from the literature[8-12] and from their practice in 1950, we can add our 1 case (Case 5) of bilateral pheochromocytomas in which 2 pregnancies occurred while the disease was active. One resulted in a normal, living baby and 1 in fetal death at six months of gestation. Thus, records are available of 7 patients with pheochromocytoma who had 9 pregnancies and deliveries. Two mothers died of shock post partum (maternal mortality, 28.6 per cent), and the fetal loss after the period of viability was 5 of the 9 (55 per cent). The diagnosis in the 2 fatal cases was not made until necropsy; both mothers went into shock early in the postpartum period. One other patient suffered from convulsions in the sixth month of pregnancy. Thus the experience available suggests that the hypertension of both Cushing's syndrome and pheochromocytoma gives high fetal risks. The maternal risk is less serious, but is still elevated for pheochromocytoma.

Pregnancy After Treatment of Cushing's Syndrome

We also have reported 5 pregnancies occurring in 5 patients (Table II) after remission of Cushing's syndrome had been induced by adrenalectomy (4 patients) or roentgen therapy to the pituitary (1 patient). Only 1 of the 5 patients had adrenal cortical insufficiency at the time of the pregnancy. In 4 patients, conception occurred one and one-half to three years after operation on the adrenal glands; in the other patient, conception occurred while she was receiving roentgen therapy to the pituitary. The urinary excretion of 17-ketosteroids and corticosteroids was low in all 4 patients who had undergone operation, but 3 did not require hormonal replacement therapy. As shown in Table II, the pregnancy of the patient who had clinical postoperative adrenal cortical insufficiency terminated in spontaneous abortion at two months of gestation, but all 4 of the pregnancies of the other 4 patients went to term and normal children were delivered without significant complications.

It is possible for pregnancy to occur in such patients under the opposing conditions of hyperfunction and insufficiency of the adrenal cortices, depending on whether conception occurs before or after bilateral subtotal adrenalectomy. This was observed in 2 of our patients (Cases 1 and 2).

Pregnancy in Patients Who Had Adrenal Cortical Insufficiency

Five pregnancies occurred in 5 patients who had adrenal cortical insufficiency (Table II). In 1 patient (Case 1) the adrenal cortical insufficiency followed operation on the adrenal glands for Cushing's syndrome due to bilateral adrenal hyperplasia and in 1 patient (Case 5) it followed adrenal operation for bilateral pheochromocytomas. Both of these patients were being treated with cortisone and desoxycorticosterone acetate by mouth at the time they became pregnant. The other 3 patients all had well-documented Addison's disease. In 2 of these 3 cases, Addison's disease in the mother became evident

for the first time post partum. A crisis occurred on the eighth postpartum day in 1 case (Case 9) and signs of adrenal failure developed gradually in the other case (Case 10) three weeks post partum and proved moderately difficult to control with substitution therapy. In these 2 cases it is probable that a destructive lesion of the adrenal cortices was present during pregnancy, although adrenal cortical insufficiency did not become clinically apparent until after delivery. The third patient (Case 11) married and promptly conceived while receiving substitution treatment for Addison's disease. Her disease was well controlled during pregnancy. An emergency cesarean section performed because of an abruptio placentae resulted in a living baby. Transient hypertension in the neonatal period was the only complication in this case. Of these 5 pregnancies which occurred in patients who had adrenal cortical insufficiency, 1 (Case 1) ended in spontaneous abortion at two and one-half months, but all the others went to term, with the delivery of normal children.

Obstetric Shock

About thirty years ago the term "obstetric shock" was applied to a then unknown group of conditions causing death immediately after delivery. During the past three decades the etiology of most of these deaths has become clear—unappreciated massive hemorrhage of various types, amniotic fluid emboli, and vascular collapse due to chronic essential hypertension are examples. Pathologic adrenal function accounts for two more: crisis of adrenal cortical insufficiency and vascular collapse of undiagnosed (or at least untreated) pheochromocytoma. There is probably one other potential cause of postpartum collapse, that is, adrenal insufficiency in a woman undergoing delivery while function of the adrenal glands is suppressed by the recent administration of cortisone. Our medical and surgical colleagues have learned this lesson, and obstetricians should be forewarned of this situation.

Supportive Measures for the Pregnant Patient With Adrenal Cortical Insufficiency

Supportive therapy should be available for use during delivery and the immediate puerperium for the pregnant patient with adrenal cortical insufficiency. If adrenal cortical insufficiency is severe, it is probably wise to employ some degree of substitution therapy during pregnancy, although, as mentioned before, patients with adrenal cortical insufficiency usually do well during pregnancy without treatment of the insufficiency.

When labor begins, it is our practice to give 200 mg. of cortisone intramuscularly. During the course of labor, a solution of cortisone and also a 1:10,000 solution of norepinephrine are kept on hand for intravenous administration if symptoms of acute adrenal insufficiency occur. During the puerperium cortisone is administered intramuscularly in decreasing dosage until the level of the patient's previous maintenance dose has been reached, whereupon the former maintenance dose of cortisone is given again by mouth. If cesarean section is planned (and therefore the patient can be prepared with cortisone over a longer period), it seems advisable to us to give the patient 200

mg. of cortisone intramuscularly forty-eight and twenty-four hours before the operation and another 200 mg. on the morning of the operation. Following the cesarean section the daily dose of cortisone is decreased gradually in a period of about a week to the preoperative maintenance dose.

If postoperative administration of norepinephrine is deemed necessary to combat hypotension, it must be given by intravenous drip and the speed of flow must be regulated individually in each case in order to maintain blood pressure at the level desired. The physician responsible for this phase of the patient's care must be in constant attendance.

Hormone Assays in Relation to Pregnancy

The values for the twenty-four-hour urinary excretion of 17-ketosteroids and corticosteroids determined for 2 patients (Cases 5 and 7) in both the nonpregnant and pregnant state are given in Table III. For Case 5, seven determinations were done on seven separate days before she became pregnant during which time she received corticotropin on five days and no hormone therapy on two. The mean value for 17-ketosteroids was 0.7 mg. and for corticosteroids 0.57 mg. per twenty-four hours. One other determination done while she was receiving 6.25 mg. of cortisone orally three times a day showed a twenty-four-hour urinary excretion of 17-ketosteroids of 1.6 mg. and of corticosteroids 0.72 mg. At the time she was eight months pregnant she was found to have an excretion of 4.9 mg. of ketosteroids in the urine in twenty-four hours, which is significantly higher than the levels obtained before pregnancy. She was taking only 6.25 mg. of cortisone by mouth three times a day at the time the urine study during pregnancy was done, and it therefore seems unlikely that the elevation of 17-ketosteroid excretion was due entirely to the ingestion of cortisone. Four days after delivery, at which time her cortisone dose had been increased to 12.5 mg. by mouth twice a day the 17-ketosteroid excretion had decreased to 2.1 mg. per twenty-four hours.

Case 7 received no hormone maintenance therapy at any time. She too had a significantly higher twenty-four-hour urinary excretion of 17-ketosteroids during pregnancy than before.

Samuels, Evans, and McKelvey[13] as early as 1943 demonstrated a significant rise in 17-ketosteroids in the urine of a pregnant patient with Addison's disease at about six months of gestation. Knowlton, Mudge, and Jailer[2] have reported 9 determinations of 17-ketosteroids in the urine of 4 pregnant patients with Addison's disease; all values were higher than usually seen in Addison's disease. In addition they found no increase in corticosteroids in the urine of 1 of these patients at eight and nine months of gestation. In a subsequent pregnancy of this patient, Jailer and Knowlton[14] found a rise in 17-ketosteroids, an appreciable rise in neutral reducing lipids and appreciable corticotropic activity in the placenta obtained at this delivery. Opsahl and Long[15] also reported ACTH activity of some magnitude in the placentas of normal obstetric patients. However, more recently Sulman and Bergmann[16] found only slight corticotropic activity in the placenta in 4 cases of normal pregnancy. As noted in the report of Case 5, studies in Dr. Albert's[17] laboratory failed to reveal

any appreciable ACTH in the placenta obtained from our patient with adrenal cortical insufficiency following the bilateral removal of pheochromocytomas.

Venning, Randall, and György[18] analyzed 3 placentas of normal women for corticosteroids, and found none. Mason[19] found only minimal amounts of formaldehydogenic corticosteroids in the placenta of 1 normal patient (90 micrograms in the entire placenta). Venning and associates[18] and Day[20] have shown that the fetal adrenal gland is not responsible for the rise in 17-ketosteroids or corticosteroids in the maternal urine during pregnancy. The question of the origin of these steroids in pregnancy is of some importance in attempting to explain the clinical impression held by many that pregnancy is beneficial in the presence of adrenal cortical insufficiency in both the human and some animal species. However, the origin of these increased urinary steroids during pregnancy in patients with adrenal cortical insufficiency is still unknown.

Summary and Conclusions

Eighteen pregnancies in 11 patients with disturbances of adrenal function have been studied. Seven pregnancies occurred in 4 patients with active Cushing's syndrome (Cases 1, 2, 3, and 4) and 2 pregnancies occurred in 1 patient with bilateral pheochromocytomas (Case 5). Five pregnancies occurred in 5 patients with adrenal cortical insufficiency (Cases 1, 5, 9, 10, and 11), of whom 3 had Addison's disease (Cases 9, 10, and 11), 1 had adrenal cortical insufficiency following surgery for Cushing's syndrome (Case 1), and 1 had adrenal cortical insufficiency following the removal of bilateral pheochromocytomas (Case 5). Four pregnancies occurred in 4 patients after treatment of Cushing's syndrome in whom no clinical adrenal cortical insufficiency was present (Cases 2, 6, 7, and 8).

Hypertension is probably the chief hazard to pregnancy in patients with hyperfunction of the adrenal cortex or medulla. Fetal loss occurred in 3 of 7 pregnancies of women in our group who had active Cushing's syndrome. Among the 9 pregnancies (2 reported here and 7 gathered from the literature) which occurred in women with pheochromocytoma, the fetal loss was 5. The hypertension of pheochromocytoma may be of serious maternal consequence, especially if the lesion is undiagnosed at delivery, since 2 of the 6 patients reported in the literature died of shock post partum.

Three adrenal states may bring about "obstetric shock" with serious postpartum collapse and death: (1) postpartum crisis in women with adrenal cortical insufficiency; (2) postpartum collapse in parturients due to a pheochromocytoma; and (3) acute adrenal cortical insufficiency after delivery of patients with induced adrenal cortical atrophy due to previous cortisone therapy. Although we have not observed this latter condition post partum, it is a definite possibility and should be borne in mind for every pregnant woman who has had cortisone therapy.

Modern treatment for adrenal cortical insufficiency properly applied to individual demands should restore good ovarian function, fertility, and ability to reproduce successfully.

Significant elevation during pregnancy of the values for urinary 17-ketosteroids and corticosteroids was found in 2 patients with adrenal cortical insufficiency. The source of the increased urinary steroids is unknown.

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Discussion

DR. WILLARD M. ALLEN, St. Louis, Mo.—This interesting paper provides plenty of opportunity for speculation. It is not surprising that patients with adrenal insufficiency should become pregnant now that satisfactory treatment is given, but it is surprising that patients with Cushing's syndrome become pregnant, when one of the cardinal signs of this syndrome is amenorrhea. But perhaps we no longer know what Cushing's syndrome is? The classical examples of this condition, those who have the moon face, the red striae on the torso and thighs, the hirsutism and the hypertension, have a relatively atrophic vaginal mucosa and amenorrhea and are certainly sterile. However, I have a feeling that the clinical diagnosis of Cushing's syndrome has become so easy nowadays that that diagnosis is rapidly becoming of little value. Almost any woman now with hypertension, some obesity, a little too much hair on some parts of her body is being tagged with a diagnosis of Cushing's syndrome. To the careless clinician, this can result only in trouble. We know of the lifesaving results that are being obtained in some cases of Cushing's syndrome by adrenalectomy or partial adrenal resection, but if extreme care is not taken in the selection of patients for this operation, many reasonably healthy women will be unnecessarily adrenalectomized. I have personally seen four patients in the past three years who would have been diagnosed by many physicians as having Cushing's syndrome whose primary pathology was in the ovaries and not in the adrenal glands at all. Two had collections of interstitial cells in the medulla of both ovaries; one had a Leydig-cell adenoma in the medulla of one ovary, and the fourth had an adrenal rest tumor. These remarks are not, in reality, a criticism of Dr. Hunt's paper. They are pertinent, however, since there will be many more patients with adrenal insufficiency subject to the hazards of pregnancy, if the adrenals are considered as readily disposable glands.

The risks of pregnancy in Addison's disease are apparently real, even though Dr. Hunt's three patients got along well. We have had two cases, both with Addison's disease prior to pregnancy. One of these patients got along satisfactorily and delivered normally, although there was considerable difficulty during the first three months. The

other patient died suddenly of an adrenal crisis at the fifth month. Pregnancy is supposed to be beneficial to the patient with Addison's disease. However, actual experience seems to indicate that there can be no relaxation of vigilance in the care of these patients during pregnancy. The finding that the 17-ketosteroid level is higher during pregnancy than when the patient is not pregnant, of course, raises the perennial question regarding the source of the steroids produced in abundance during pregnancy. The pregnandiol and the estrogen certainly do not come from the adrenal. In our patient who survived and who had had typical Addison's disease for about four years prior to the pregnancy in question, the levels of pregnandiol and estriol were normal. Samuels has made similar observations, probably on one of Dr. Hunt's cases. We have found in two cases of abdominal pregnancy, where the fetus was removed and the placenta left in situ, that pregnandiol continues to appear in the urine for three weeks. This experiment would seem to exclude the adrenals and gonads of the fetus. Likewise removal of the ovaries after the third month does not affect the production of pregnandiol or estriol. In short, the available evidence supports the prevalent idea that the placenta is the extragonadal source of these two steroids. It requires no great stretching of my imagination to make me believe that the increase in ketosteroids in the pregnant patient with Addison's disease is due to the production of some steroid by the placenta which appears in the urine as a ketosteroid.

DR. RUSSELL DE ALVAREZ, Seattle, Wash.—I wish to say a word about DOCA in the therapy of this condition. We have found that DOCA produces a decrease in filtration rate at the glomerulus, a decrease in urinary output with increased antidiuretic substance, and increased sodium reabsorption. This raises the question of edema formation and retention of sodium and water and, therefore, the desirability of the use of DOCA even in Addison's disease. However, because these patients do not have the ability to retain sodium and water in amounts required to sustain health and life, they need some substitute to carry out this function. One may, therefore, use cortisone or hydrocortisone alone without DOCA because of the sodium-retaining properties of these two hormones, inasmuch as patients may be carried on relatively small maintenance doses, even though completely adrenalectomized. However, when cortisone or hydrocortisone is given, the addition of sodium chloride is required. In this way, the metabolism of sodium chloride more nearly approximates that of normal values.

We have under our care a 33-year-old patient with adrenal hyperplasia who never menstruated. During the period of study and treatment with cortisone pregnancy was suspected by a sustained elevation of the basal body temperature and confirmed by conventional methods. Throughout her pregnancy she was continued on cortisone and there was no change in the serum electrolytes, the chorionic gonadotropins remained normal throughout the pregnancy, and the pregnandiol excretion was normal, having risen to above 20 mg. daily by the third month. The 17-ketosteroids showed no change during pregnancy. Our patient was treated only by medical measures and was essentially adrenalectomized by the use of cortisone.

I should like to ask Dr. Hunt whether he feels it desirable to adrenalectomize these patients surgically or whether it would be possible to carry them on small doses of cortisone, particularly where evidence of tumor can be ruled out. If so, what might be the smallest dose of cortisone to use if he wishes to limit 17-ketosteroid excretion, and at what level would he keep the 17-ketosteroid excretion if he were to treat that alone?

DR. HUNT (Closing).—I congratulate Dr. Allen for seizing on the condition of abdominal pregnancy to do a nice experiment. However, if we look for both Addison's disease and abdominal pregnancy in the same patient it will be a long time before we have much to report.

I, too, wonder about the infrequency of menstruation and fertility in the presence of Cushing's syndrome. It is rare and that is why we have so few cases to talk about.

I am grateful to Dr. de Alvarez for pointing out the difficulties connected with the use of DOCA, because they are evident in nonpregnant patients too. We did use DOCA

in these patients who required treatment during pregnancy, but watched the sodium very carefully and watched the dose carefully. There was no difficulty from its use. I think his suggestion of using sodium chloride and cortisone is good. I cannot say that the treatment of Cushing's syndrome by cortisone has been very effective with our group. Dr. Allen's point that these hormone assays are not precise is a good one, and I think it would apply not only to 17-ketosteroids but to corticosteroids. Dr. Davis presented informally a case of bilateral adrenalectomy in pregnancy and he had extensive hormone determinations which parallel our findings with increased 17-ketosteroids and corticosteroids in pregnancy.

I would like to show four slides of two of these patients with Cushing's syndrome. The picture on the left is prior to bilateral subtotal adrenalectomy and on the right is after treatment. This woman became pregnant postoperatively. The next slide shows the lateral view and the hirsutism, buffalo hump, and other features that go with Cushing's syndrome. The next slide is a lateral view, and the woman is not pregnant. The last slide depicts the woman who had had four pregnancies before operation; it presents classically the type of obesity seen in Cushing's syndrome.

THE VASCULAR BED OF THE BULBAR CONJUNCTIVA IN THE NORMAL MENSTRUAL CYCLE*†

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DURING the normal menstrual cycle, there is considerable evidence of widespread vascular changes in a variety of tissues throughout the body. Extragenital bleeding is not uncommon. Roth[1] in 1920 reported vicarious menstruation from several sources; epistaxis was the most frequent type encountered among the 255 cases studied. Hemoptysis several days before the menses was also recorded on a few occasions. Kieser[2] has described hemorrhages from the nose, rectum, lung, and urinary bladder, while Saitz[3] observed small hematomas of the urinary bladder near the trigone during physiological uterine bleeding. It has been the impression of many gynecologists that more bleeding is encountered in operations performed during the premenstrual phase as compared to other periods of the cycle. Frank[4] stated that occasionally, during the premenstrual phase, subcutaneous hemorrhages of the flexor surfaces of the thighs and forearms occurred. Thus, varying degrees of a hemorrhagic diathesis, while by no means the rule, may be encountered prior to or during menstruation. Further evidence of circulatory, electrolyte, and tissue changes is demonstrated by the frequent presence of rather minimal degrees of premenstrual ankle and pretibial edema or swelling of the eyelids. Slight changes in the voice noted particularly by singers are apparently caused by edema and increased vascularity of the vocal chords.

In addition, certain abnormal states have exacerbations often associated with the premenstrual phase of the cycle. Migraine and tension are frequently encountered at this time. In the opinion of Wolff[5] the headache phenomenon is the result of distention of the intracranial arteries. Bulkley[6] reported the frequent appearance or recurrence of areas of eczema two to three days prior to the menstrual bleeding. Koch, Escher, and Lewis[7] recently stated that the bleeding in hereditary hemorrhagic telangiectasis appears commonly five days prior to menses, and was prevented in several instances by small doses of estrogens.

It is apparent from these observations that evidence of peripheral vascular changes during the menstrual cycle is largely indirect, inferred from

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manifestations of bleeding, edema formation, and weight change. The vessels in the transplanted endometrium in the macaques have been studied but to the best of our knowledge direct observations of capillary and arteriolar vessels in the human bulbar conjunctiva during menstrual cycles have not been hitherto reported. Specialized techniques, recently developed for the direct observation and measurement of changes occurring in the vascular bed of the bulbar conjunctiva,[8] have added to our knowledge concerning these peripheral phenomena in normal pregnancy and essential hypertension. Because of the indirect evidence of vascular changes during the menstrual cycle mentioned above, an investigation of the conjunctival vessels was undertaken. The examinations were performed at frequent intervals during the normal menstrual cycle in healthy young women to determine whether or not any significant venular, arteriolar, or capillary differences are detectable.

Methods

The bulbar conjunctiva of 15 normal women between the ages of 18 and 36 years were viewed daily during the complete menstrual cycle with a slit lamp and binocular microscope. Basal body temperature, the daily weight, and the interpretation of vaginal smears in some were recorded to confirm the presence of a normal cycle. These data, along with the duration of menstruation, the presence of dysmenorrhea, ovulatory pain, etc., indicated that all these cycles were essentially of the normal ovulatory type. One subject developed a cold during one secretory phase which produced marked vascular changes and accordingly these observations were excluded. The slit lamp binocular observations were made at approximately the same time of day under uniform temperature and light and by the same observers. Representative photographs were taken of the same vessels at different phases of the menstrual cycle with a 35 mm. camera and a Strobe flash unit of 180 watt seconds. It is estimated that we made over 1,600 observations and took 700 photographs to record and document the changes observed. The photographs illustrating the vascular beds are magnified 150 times.

In the peripheral vascular bed of the bulbar conjunctiva, specific terms are used to define and to designate accurately the changes observed. Vasomotion is a wavelike undulating motion noted along the course of the fine arterioles. In a more advanced degree of the same activity, it is described as mild spasm, Grade I. When true bulbs are present and further thinning of the arteriole is evident, it is defined as Grade II spasm. A generalized reduction of the caliber of the arteriole is called attenuation. At certain times the blood flowing through the vascular bed is reduced and if the capillaries are relatively emptied of blood, the condition is referred to as ischemia. A decreased rate of flow in the venules is manifested by a granular appearance of the blood column which is arbitrarily graded as to degree. This same phenomenon in the arteriole is more appropriately described as segmented flow. At times, in the small venules, aggregated groups of red blood cells separate from clear areas of plasma giving a detached appearance. The sensitivity of the terminal arterioles is determined by the instillation of diluted epinephrine hydrochloride into the conjunctival sac. The minimal dilution causing constriction is designated as the epinephrine end point. Dilutions used range from $\frac{1}{10,000}$ to $\frac{1}{500,000}$. Previous studies indicate the average reactivity in the normotensive adult is from $\frac{1}{30,000}$ to $\frac{1}{100,000}$ dilution of epinephrine.[8]

Results

In the 15 subjects under study the menstrual cycles varied in duration from 25 to 37 days. Daily observations of the conjunctival vascular bed were made over one complete cycle in 4 and over 2 or more cycles in 11. These results include a total of 35 menstrual cycles. Many other candidates were studied but for various reasons complete observations could not be made and accordingly the results are not included.

During the normal menstrual flow the arterioles exhibit a marked reduction in the rate of blood flow and, on occasion, scattered segmentation is seen. The arterioles are thin, attenuated, and vasomotion may be greatly accentuated. In 3 subjects this vasomotion was so marked that it was classified as Grade I spasm. The venules become less vascular and narrower than during other phases of the cycle. Blood flow is likewise slow and granularity in the venules of a Grade I degree is frequent and, in several instances, granularity of Grade II is visualized. The capillary bed becomes ischemic, the rate of blood flow is slow, and the blood has a granular appearance. The epinephrine end point during early menstruation is at a high normal of $1/100,000$ dilution. Some, although not all, of these changes may be seen in all subjects observed during menstruation. These variations are more obvious at the onset of menses and usually recede after the third day.

The following 3 to 5 days represent a transitory phase. There is a gradual increase in vascularity; the rate of blood flow becomes more rapid; segmentation, granularity, vasomotion, and ischemia are reduced. From this period to the approximate time of ovulation, the arterioles are filled and the rate of flow increases. Vasomotion is absent or slight and the caliber of the vessels is average. Venules are filled and without granularity and the rate of flow is accelerated. The capillary bed shows no ischemia or granularity. The epinephrine response during this proliferative phase is reduced to $1/50,000$.

Primarily by means of basal body temperatures and confirmed in some instances by ovulation pain and vaginal smears, the time of ovulation was approximated. During this period of 24 to 48 hours, certain minimal, inconstant vascular phenomena may be observed. The blood in the arterioles exhibits slight slowing and there is a mild increase in vasomotion and constriction. In the venules and capillaries there is minimal evidence of slowing, granularity, and ischemia. The epinephrine reactivity remains unchanged.

During the secretory phase the arterioles progressively become dilated and filled. The rate of blood flow increases. Vasomotion is absent in the earlier portion of this period. The venules are engorged and without granularity. The capillaries are filled and also without granularity or ischemia. At about the middle of this secretory period, vasomotion begins and becomes more prominent as the menstrual cycle is approached. Also, the blood flow gradually becomes slower with a progressive increase in granularity, but the vessels remain dilated and engorged. The epinephrine reactivity remains unchanged at $1/50,000$ dilution. Thirteen of the 15 subjects demonstrated engorgement at this period.

From 1 to 3 days prior to the onset of and including the first 2 days of menstruation, there is a period of arteriolar vasoconstriction and reduced blood flow in all vessels. The arterioles appear attenuated and characteristically at this stage vasomotion becomes maximum. The flow in the venules and capillaries is slow with prominent granularity and ischemia. The epinephrine reactivity end point increases during this constricted phase, averaging $1/100{,}000$ dilution.

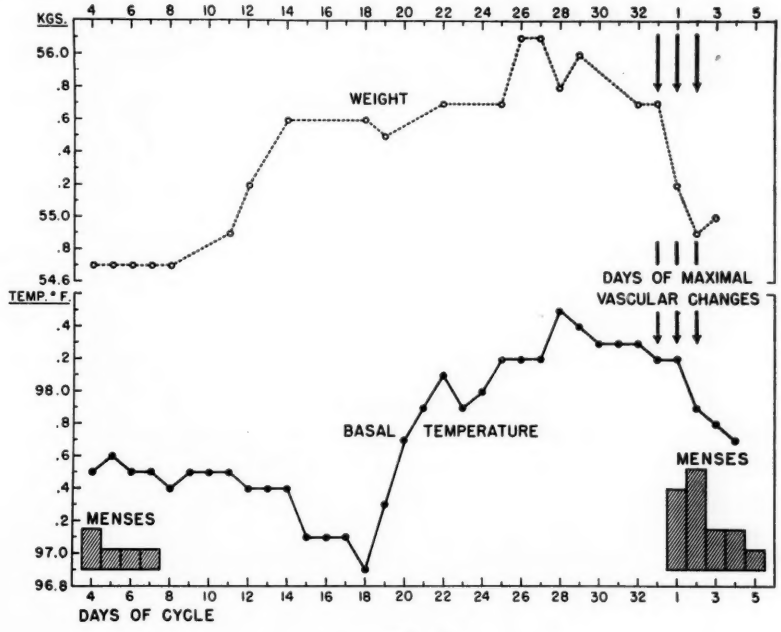

Fig. 1.

In 9 full cycles daily weights were recorded. In 7 there were significant variations; weight loss usually occurred in the interval from the first premenstrual day to the second day of the cycle. The average weight loss is 1.0 kilogram, with a maximum at 1.5 and the minimum at 0.5 kilogram. Usually the weight loss immediately follows the development of maximal constriction in the vessels of the bulbar conjunctiva. Fig. 1 shows the relationship in the menstrual cycle of weight and temperature alterations to the time of maximal conjunctival vascular reaction in one typical subject. The vascular phenomena of arteriolar slowing, marked vasomotion, and increased granularity in the venules usually occur at about the same time as the temperature fall.

This general pattern of vascular bed activity is found to vary quantitatively from one patient to another. Likewise, it is evident that quantitative differences exist in the same subject from one cycle to another. The same intrinsic variation which may occur at the time of ovulation and menstruation exists for the vascular bed patterns.

TABLE I

STAGE OF CYCLE DAY	MENSTRUAL 1-4	PROLIFERATIVE 2-13	OVULATORY 12-17	SECRETORY 16-30	PREMENSTRUAL 21-37
Arterioles.—					
Appearance	Vasomotion	Filling	Slight vasomotion	Filled	Vasomotion
Rate of flow	Slow	Faster	Slower	Fast	Slow
Diameter	Attenuation	Average	Slight constriction	Dilatation	Constriction
Venules.—					
Appearance	Granular	Filling	Slight, granular	Engorged	Granular
Rate of flow	Slow	Faster	Slower	Fast	Slow
Diameter	Thin	Average	Average	Dilatation	Thin
Capillaries.—					
Appearance	Granular, ischemia	Filled, no granularity	Slight ischemia Slight granularity	Filled, no granularity	Ischemia, granular
Rate of flow	Slow	Faster	Slower	Fast	Slow

Table I summarizes these variations in the bulbar conjunctival vascular bed seen over the course of a normal menstrual cycle. Figs. 2 and 3, G. D. (30 day cycle), show the arterioles and venules in the postovulatory and late secretory phases, respectively. The dilatation of the arteriole and the engorgement of the venule in the latter phase are readily demonstrable. Figs. 4 through 7 depict the conjunctival vascular bed of D. K. (27 day cycle). Fig. 4 is the day prior to the onset of menses. The constriction of the arteriole, vasomotion, the thinning of the venules, and the capillary ischemia are typical of this premenstrual period. Fig. 5 is the third day of the cycle. Already there is some reduction of the vasoconstriction, but vasomotion continues. The venule is slightly wider and ischemia remains but to a lesser degree. Fig. 6 is day 13 considered to be following ovulation. The arteriole is dilated and vasomotion is absent. The venules and capillaries are well filled without ischemia. Fig. 7 illustrates the late secretory or early premenstrual phase, day 25 or two days prior to menstruation. The arteriole remains slightly dilated with some vasomotion. The venule is engorged but there is an increase in granularity. The capillaries exhibit a moderate ischemia.

Comment

There were considerable variations in the changes of the vascular bed in the different subjects studied. Many authors have indicated that variations exist in the peripheral vascular bed during the different phases of the menstrual cycle. Brewer[10] in 1938 reported the rhythmical changes in the skin capillaries in relation to menstruation. By applying a vacuum to the skin at various pressures he was able to observe differences in pressure necessary to produce hemorrhage. Capillary hemorrhages were obtained most easily in the normal subject on the first day of the menstrual cycle. After the second day of the cycle, the capillaries became more resistant to the pressure and the hemorrhages were more difficult to produce. In the premenstrual phase,

there usually was an increase in capillary fragility reaching a maximum on the first day of the cycle. Stephan,[11] using the Rumpel-Leede phenomenon, also noted that capillary hemorrhage was more easily produced during the menses.

Fig. 2.

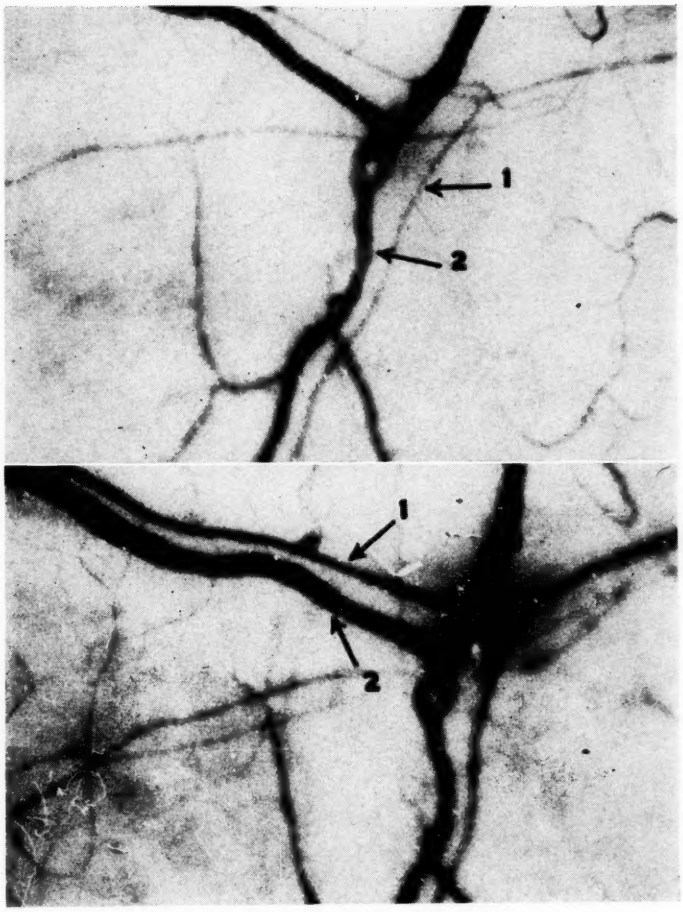

Fig. 3.

Fig. 2.—G. D. Day 18. Thirty-day cycle. *1*, artery, and *2*, venule. Average.
Fig. 3.—G. D. Day 26. *1*, artery, and *2*, venule. Vasodilatation and engorgement.

The most striking and most consistent of our findings was the arteriolar dilatation during the week prior to the menses resulting in the so-called granular appearance in the venules. This varies in onset from 3 to 12 days prior to menstruation. The granular capillary bed was first described by Zilliacus,[9] who suggested the presence of this variation in the conjunctival vessels during the menstrual cycle. At or about ovulation the most frequent finding was an increased spontaneous vasomotor activity of the arterioles and some slight ischemia of the capillary bed.

The granular capillary bed, the increase in vasomotion, and the reduction of arteriolar size immediately prior to or at the onset of menstruation indicate that vasospasm produces these observed variations in the conjunctival bed. Hagen[12] in 1922 observed, by the use of the capillary microscope, spasm in

Fig. 4.

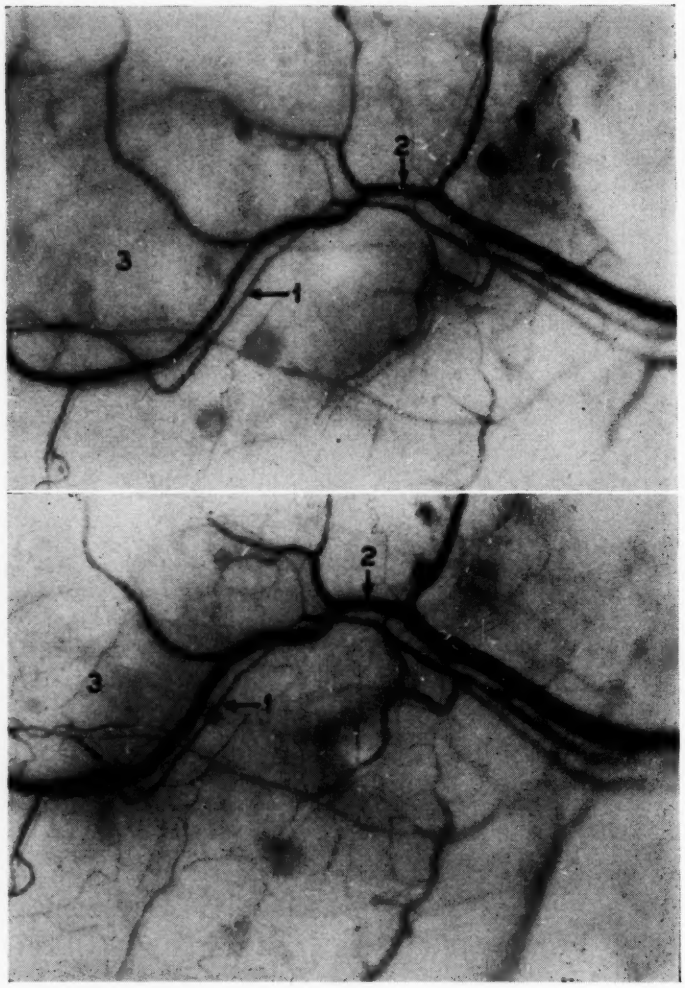

Fig. 5.

Fig. 4.—One day prior to menses. Twenty-seven-day cycle. *1*, artery, constriction, vasomotion. *2*, venule, narrow, slow. *3*, capillary, ischemia, slow.

Fig. 5.—D. K. Day 3. *1*, artery, slight constriction, vasomotion. *2*, venule, wider. *3*, capillary, less ischemia.

the skin vessels during the premenstrual period. The increased sensitivity to topically applied epinephrine at the onset of menstruation is strongly suggestive of an intrinsic vasospastic predisposing state.

The fundamental observations of Markee,[13] Bartelmez,[14] Okkels,[15] and Daron[16] revealed that the uterine arterioles manifest vasodilatation during the premenstrual phase and vasoconstriction at the onset of menstruation. Markee's[17] work on monkeys with transplanted endometrium in the anterior

chamber of the eye indicated most clearly that the primary tissue receptor, the uterine endometrium, responds to the ovarian cycle by a vasodilatation one to five days prior to menstruation and a vasoconstriction four to twenty-four hours prior to the escape of endometrial blood. The previous indirect observations of Brewer and others and the present direct study of the con-

Fig. 6.

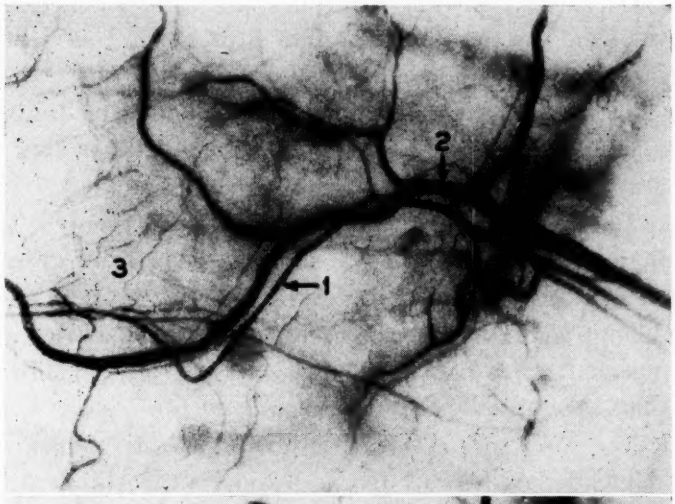

Fig. 7.

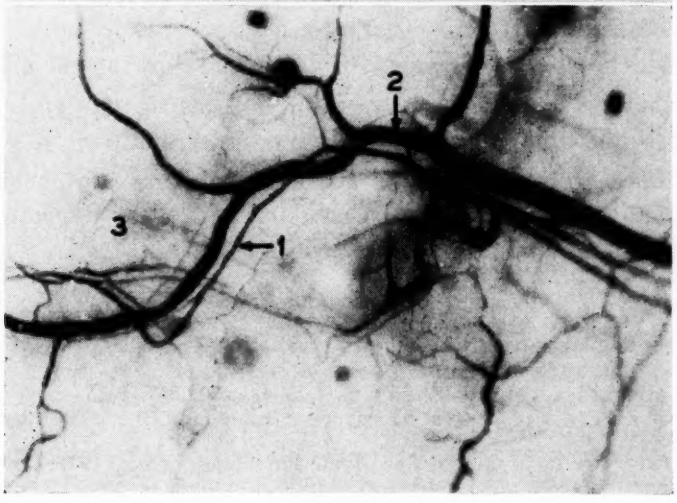

Fig. 6.—D. K. Day 13. *1*, artery, dilatation, no vasomotion, fast. *2*, venule, full, fast. *3*, capillary, no ischemia, fast.

Fig. 7.—D. K. Day 25, or two days prior to menses. *1*, artery, slight dilatation, slight vasomotion. *2*, venule, engorged, granularity, slow. *3*, capillary, increased ischemia.

junctival vascular bed in the human being demonstrate that cyclical changes in the peripheral vessels do occur and are probably widespread in nature. It would seem reasonable to suppose that they are responsible in part at least for the readily demonstrable general systemic vascular and tissue changes that occur during the various phases of the menstrual cycle.

Conclusions and Summary

1. The circulation of the bulbar conjunctiva may be observed during the normal menstrual cycle without difficulty through the slit lamp microscope at a magnification of 50×. Accurate determinations can be made of the velocity of capillary blood flow, vessel characteristics, and their reaction to pharmacological agents.

2. During menstruation the arterioles are constricted and attenuated with very prominent vasomotion. The flow of blood in the venules and capillaries is slow and granular and the capillary bed is ischemic.

3. From day 3 of menstruation to about the time of ovulation, there is a progressive increase of vascularity in all vessels. Blood flow is faster and vasomotion, granularity, and ischemia recede or are absent.

4. At the time of ovulation, in some instances, there is an increase in vasomotion in the arterioles with some slight ischemia and granularity in the capillaries and venules.

5. From about ovulation to the week prior to menstruation, there is a general engorgement and dilatation of all vessels. Blood flow is fast while granularity and vasomotion are minimal.

6. During the week prior to menses, vasomotion reappears, granularity increases, and blood flow slows but the vessels remain dilated and engorged.

7. Immediately prior to menstruation a vasoconstriction of the arterioles takes place which usually continues for 48 hours following the onset of menses.

8. The changes described are variable both as to time and degree within the same subject as well as from individual to individual.

9. The increase in epinephrine sensitivity during the constrictive phase suggests a change in the terminal vascular bed and is associated with vasomotion, vasoconstriction, and blood slowing.

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Discussion

DR. J. ROBERT WILLSON, Philadelphia, Pa.—The cyclic alterations in activity of the conjunctival vessels and in the blood flow through them which were demonstrated by this study are much like those observed in the vessels of endometrial tissue transplanted into the eyes of monkeys. According to Douglas and his colleagues, vascularity is increased, blood flow is fast, and vasomotion and granularity are decreased during the estrogenic and the early progestational stages of the cycle. During the late secretory phase, marked vascular dilatation and engorgement are evident. As the hormone levels fall premenstrually, vasoconstriction appears. In transplanted endometrium Markee noted a progressive increase in the number of open capillary loops, in erythema, and in rate of blood flow during the proliferative stage, but after ovulation occurred the flow rate gradually decreased until almost complete stasis was present just prior to menstruation. He postulated that the intracapillary pressure must be elevated during the estrogenic phase, otherwise an increased flow through a greater number of patent vessels could not occur. The stasis during the corpus luteum phase suggests that the pressure at this time is decreased.

Although the study provides direct evidence that the circulatory changes during the menstrual cycle in women are widespread and not confined to the endometrial vessels and suggests that activity of the estrogenic hormone is responsible for the high rate of blood flow and the absence of stasis, the exact method by which these changes are mediated and the reasons for their occurrence are as yet unanswered.

It is interesting to speculate upon the possible relationships between the observed conjunctival circulatory changes and cyclic alterations in hormone levels and in basal temperature. An increased rate of flow, like that noted during the first half of the human cycle accompanied by a fall in skin temperature, can be produced in the ear of a castrated rabbit by the administration of estrogen, and in the human being the thermogenic effect of progesterone is well established. Since body temperature is in part regulated by alterations in blood flow through superficial vessels, it is possible that the marked vasodilatation and the reduced flow during the second half of the cycle, when the basal temperature is elevated, may represent a thermoregulatory mechanism.

One might also raise the question as to the method by which these changes are produced. Although the steroid hormones are known to have a direct action upon certain tissues, notably the vaginal epithelium, a similar effect upon blood vessels has not been substantiated and any action they have may be secondary to their stimulation of some other structure. Acetylcholine, for instance, is thought to possess the ability to open the arteriovenous anastomoses in the endometrium, thereby producing congestion and diminished blood flow through the mucosal vessels. Since Reynolds was able with estrogen to produce marked nasal mucosal hyperemia which he attributed to the production of acetylcholine, a similar effect might be responsible for the changes observed in the conjunctival vessels. Woodbury found that the injection of Pitressin caused arteriovenous shunts in the skin vessels of dogs to dilate; this effect could be prevented by pretreatment with stilbestrol. In untreated rabbits, the injection of Pitocin produced a fall in blood pressure, but after the same animals had been given stilbestrol, the vascular system became so sensitive that the minute amount of Pitressin contaminating the oxytocic principle caused the pressure to rise.

Although the full implications of this study are not as yet obvious, it is possible that, after the reasons for the conjunctival vascular changes are better understood, the study of these vessels may become an important aid in the evaluation and treatment of certain gynecologic disorders.

DR. LANDESMAN (by invitation).—A review of the observations presented here clearly indicates that some differences were detectable in almost all patients, particularly in the late premenstrual phase and the first few days of the menstruation. Slight movement of the eyes, poor focusing, and light streaks were some of the sources of difficulty.

Usually two minutes were required to take three photographs of the same vascular field, and also multiple pictures demonstrated that no vascular change occurred because of the light used in the exposure. Complete magnification of the field is 150 times; magnification of an ophthalmoscope is 16 times.

Where do these observations lead us from this point? It is true that to some extent these vascular changes vary from individual to individual. Maximal variations occur in some and only minimal changes in others. What produces these changes? Can they be reproduced in the same way as other findings are? Will progesterone and estrogen produce these variations? Are these extragenital findings more evident with the uterus out? What occurs in the menopause? Does this cyclic pattern persist during the early months of pregnancy? These are some of the problems at present under investigation; further study may clarify some of them.

DR. DOUGLAS (Closing).—We have not ventured to express any opinions concerning many practical possibilities that come to mind. We have purposely avoided conjecture in this report and have only presented the objective findings. We are greatly interested, for instance, in the sudden decrease in weight and basal body temperature which coincides with the onset of menstruation which occurs at the time of maximal vascular changes. It is also significant that at this time the premenstrual syndrome experienced by so many women usually promptly disappears. We are not prepared to say whether there is any causal relationship between these phenomena and the associated vascular changes.

THE RELATIONSHIP OF HORMONAL ENVIRONMENT TO THE GENESIS AND TO THE INHIBITION OF NEOPLASTIC GROWTH: IS CANCER AUTONOMOUS?*

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LAST fall when your President invited me to occupy this enviable spot on your program, he suggested that I discuss hormonal environment as it pertains to the growth of certain neoplasms. The full title that we agreed upon probably could be improved. However, the question that we ask in the title, "Is cancer autonomous?" I believe is now an appropriate one. As a medical student I was taught that cancer is an autonomous or parasitic growth beyond the control of any physiologic mechanisms, a hopeless concept that I found to be one for the defeatists. Indeed, I believe that I was attracted to the field of cancer research by a skepticism for those teachings and by the early experimental observations which suggested that certain tumors developed as the result of abnormal hormonal environments. Today, as a result of the many studies which are in the literature and which are now in progress in many laboratories, I believe that we can justifiably challenge that old concept. Indeed, I believe that studies on the relationship of hormones to the development of tumors or to the inhibition of certain metastatic neoplasms make it possible now for us to foster a real hope for eventual control of these diseases by physiologic means.

The medical and biological literature of the last decade and a half is replete with experimental and clinical studies on the relationship of hormones to neoplasms. Such intense activity in this field during the past 15 years can be attributed to the availability of potent synthetic and natural hormones and to experimental tools and techniques not previously available. To review by brief reference to this vast literature would require much more time than that allotted me this evening. There are, however, excellent reviews on this subject by Loeb,[1] Gardner,[2] Shimkin,[3] and Nathanson[4] which I can recommend to you.

Before discussing some of the modern studies, it should be pointed out that in 1889 Schinzinger,[5] a German surgeon, advocated oophorectomy in premenopausal women with cancer of the breast because of the atrophy of the breast which follows loss of ovarian function. A few years later in 1896 Beatson,[6] a surgeon from Glasgow, reported striking beneficial changes in two premenopausal women with extensive and metastatic cancer of the breast whom he had oophorectomized and treated with thyroid.

*Address of the Guest Speaker, presented at the Seventy-sixth Annual Meeting of the American Gynecological Society, Lake Placid, N. Y., June 15 to 17, 1953.

Hormonal Factors in the Production of Tumors in Experimental Animals

The first carefully planned and executed study of the glands of internal secretion and their relationship to cancer was that reported in 1919 by Dr. Leo Loeb.[7] He demonstrated in mice having a high incidence of breast cancer that ovariectomy of the young prevented the development of mammary cancer. Castration after the age of 6 months had practically no effect on the development of these tumors.

In 1932, Lacassagne[8] first succeeded in producing carcinoma of the mammary gland in male mice belonging to high tumor strains by injecting large amounts of estrogenic hormones over long periods of time. Negative results were obtained when estrogens were administered to male mice belonging to strains in which spontaneous mammary tumors in the females are uncommon. These experiments were confirmed very promptly by Burrows,[9] and Gardner, Smith, Allen, and Strong.[10]

Since that time there have been many reports of tumors produced in animals after prolonged treatment with various estrogenic compounds both steroidal and nonsteroidal.

Lacassagne[11] has demonstrated that the influence of various estrogens on the formation of breast tumors in mice appears to be proportional to their estrogenic activity. Gardner[12] has reported that the administration of estrogens to hybrid mice from matings of high tumor strains and low tumor strains resulted in a high incidence of tumors in mice whose mothers were of the high tumor strain but not in those whose mothers were of a low tumor strain.

Gardner, Allen, Smith, and Strong[13] reported in 1938 the appearance of a metastasizing transplantable cancer of the cervix in a mouse of a high tumor strain following the injection of estrogens for 10 months. Subsequently, Allen and Gardner[14] have produced several cancers of the cervix in two groups of hybrid mice.

Lipschütz, Rodriguez, and Vargas[15] have reported that the administration of estradiol monobenzoate to guinea pigs resulted in the development of uterine and extrauterine fibroids and endometrial polyps which extended into the vagina. They[16] have reported subsequently that the simultaneous administration of testosterone or progesterone with the estrogen prevented the development of such uterine fibroids.

Gardner, Dougherty, and Williams[17] have studied the lymphoid tissues of seven strains of mice which received estrogens over a long period of time. In three strains (C3H, CBA, P.M.) they have observed 15 per cent incidence of lymphosarcomas, in the other strains (C 121, JK, A, and C 57) they have observed an incidence of 2 to 5 per cent. It is of interest that the simultaneous administration of testosterone with estrogens in one of the more susceptible strains was observed to result in an apparent inhibition of the development of such lymphoid tumors.

Hooker and Pfeiffer[18] have reported that the administration of estradiol benzoate or of stilbesterol to male mice of the A strain resulted in the development of interstitial-cell tumors of the testes which apparently were capable of producing androgens. They postulated that the mechanism of this tumor's genesis was through a stimulatory effect on the pituitary's production of luteinizing hormone, which in turn acted to stimulate growth of the Leydig cells.

Wooley and his associates[19, 20, 21] have followed male and female mice of several strains, which were castrated between 1 and 6 months of age. In these animals they have observed hyperplasia and neoplastic changes in the adrenal cortices. Some of these tumors were observed to exert androgenic effects on the hosts and others exerted estrogenic effects. In several of their mice tumors of the mammary glands and of the pituitaries were observed after the development of the adrenal tumors.

Leo Loeb[22] was the first investigator who explored the role of the pituitary in the development of mouse tumors. In 1939, Loeb and Kirtz reported that they had successfully transplanted pituitaries of inbred mice to their siblings. Such transplants caused marked development and secretory activity in the mammary glands. They caused a marked increase in the incidence of mammary tumors. In a small number of mice with transplants of the anterior pituitary, precancerous changes were observed in the vaginal cervical tract.

In 1941, Evans and his associates[23] reported that the administration of pituitary extracts rich in gonadotrophic hormones caused placentomas in normal but not in hypophysectomized rats. A pituitary preparation rich in lactogenic hormone favored the production of such tumors in normal, adrenalectomized, or hypophysectomized rats, but not in ovariectomized animals.

More recently, in a series of important studies, Moon and associates[24, 25, 26] have reported that the prolonged administration of growth hormone to intact rats of the Long Evans strain resulted in the development of lymphosarcomas of the lung and of the peribronchial lymph nodes, of solid tumors of the ovaries, and of atypical hyperplasia of the ovarian follicles which resembled granulosa or interstitial-cell tumors of the ovary. Fibroadenomas of the breast occurred more often and were larger than in the untreated controls. In the adrenals of these animals the adrenal cortices showed nodular changes and the medullas were hypertrophic and proliferative with areas of neoplastic cells invading and displacing the adrenal cortices. In three rats the neoplastic medullary tissue grew through the cortex and was macroscopically visible on the surface of the adrenal gland.

The pituitaries of these animals were found to contain smaller, less granular, and fewer acidophils than those of the controls, while the basophils were increased in number and resembled those observed in castrate rats. In one rat, the pituitary contained numerous small basophilic adenomas.[27]

It is of interest that the administration of growth hormone to hypophysectomized rats of the same strain resulted in a normal growth response but

failed to produce any neoplastic changes.[28] This obviously suggests that some other pituitary hormone or a hormone of the target gland of some other pituitary hormone is necessary to the development of such tumors. More recently these same investigators[29] have reported that the development of cancers in response to treatment with methylcholanthrene is markedly diminished in hypophysectomized rats.

During the past decade, we have had a variety of goitrogenic agents made available. These agents are goitrogenic by virtue of two actions, i.e., secondary to a hypothyroidism, which they produce, they cause an increased secretion of thyrotrophic hormone (TSH) by the pituitary, and they enhance the action of TSH. With these agents at hand, several investigators have administered them to rats or mice over long periods of time. In 1944, Bielschowsky[30, 31] reported that the administration of 2-acetyl-aminofluorine and allyl thiourea to rats resulted in the production of thyroid tumors, both benign and malignant. Shortly afterward, Griesbach, Kennedy, and Purves[32] reported that the administration of a rape seed diet resulted in the development of hyperplastic goiters which later manifest tumors of the thyroid. More recently, these same investigators[33] have produced a highly malignant cancer of the thyroid by administering methyl thiouracil to their rats.

Dalton, Morris, and Dubnik[34, 35] have reported that the administration of thiouracil to mice of a high tumor strain resulted in the development of metastasizing and transplantable cancers of the thyroid, whereas the same agent, when administered to mice of a low tumor strain, produced hyperplasia and benign tumors of the thyroid. Money and Rawson[36, 37, 38] have observed that the administration of thiouracil to rats of the Sprague-Dawley strain resulted in a variety of benign adenomas. When they combined thiouracil with subcutaneous injections of dibenzanthracene, they were able to produce a transplantable cancer of the thyroid. It is concluded that such cancers are dependent on the growth stimulus of the pituitary thyroid stimulating hormone and upon an inherited cancer susceptibility or the coaction of a carcinogen.

Observations Suggesting Possible Hormonal Factors in Genesis of Human Cancer

It would be premature to conclude from the above experimental observations that these various hormones are a cause of cancer as seen in man. However, it would be quite unsound to discard them as of no consequence in human studies. Indeed, there are several clinicopathologic states, recently described by thoughtful and observing students, which give credence to the theory that similar situations might apply in man.

In 1922, Schröder of Rostock[39] reported on a 45-year-old patient in whom he had found a large granulosa-cell tumor of the ovary, which was associated with endometrial hyperplasia and an early carcinoma of the endometrium. Dockerty[40] and Hodgson, Dockerty, and Mussey[41] have reported a variety of pathologic lesions which coexisted with granulosa-cell tumors in 62 patients

seen at the Mayo Clinic. Thirty-two (51.6 per cent) of these feminizing tumors were associated with uterine fibromas, 8 (or 12.9 per cent) with carcinoma of the uterine fundus, and 3 (or 4.8 per cent) with carcinoma of the breast. Banner and Dockerty[42] have reported that in 23 patients with thecal-cell tumors myohypertrophy and/or fibromyomas were found in 13, endometrial adenocarcinoma in 3, adenoacanthoma of the cervix with metastases in one and epidermoid carcinoma of the cervix in one. More recently Dockerty and Mussey[43] have reported that the incidence of endometrial cancer in a series of 87 patients with granulosa-cell or thecal-cell tumors was more than 15 per cent. In 3 of their patients endometrial and breast carcinomas were found to exist or to occur shortly after the ovarian tumors had been removed. Smith[44] has stated that one-fifth of his patients with granulosa-cell tumors also had endometrial cancers. Smith[45] has also noted a cortical stromal hyperplasia in the ovaries of 80 per cent of his postmenopausal patients with endometrial cancer. This cortical stromal hyperplasia has been described as an increased thickness and cellular density in the cortical stroma with numerous whorls and interlacing fascicles weaving about variable numbers of capillaries and dipping irregularly into the relatively cellular eosinophilic medullary stroma. Enlarged nuclei with abundant coarse granular chromatin have been described in these cortical stromal cells. Because these structures take fat stains it has been suggested that they represent estrogen-secreting tissue. This hypothesis will have to be proved by isolating the hormone from the tissue or from the venous blood of such ovaries. In subsequent studies by Woll, Hertig, Smith, and Johnson[46] the incidence of cortical stromal hyperplasia in patients with endometrial cancer was found to vary in various decades between 56 and 92 per cent whereas for a control age group it was found to vary between 36 and 43 per cent. These investigators also reported that thecomas in patients with endometrial cancer are 9 times as common as in a control group.

In view of the fact that the growth hormone, which at the present time appears to be identical with the diabetogenic hormone, when administered to rats over a period of months produced ovarian tumors which resembled granulosa- or interstitial-cell tumors, it is interesting that Moss[47] observed mild to severe diabetic glucose tolerance curves in 20 of 23 patients with endometrial cancer.

Sommers and Teloh[48] have reported that cortical stromal hyperplasia was observed in 83 per cent of 100 autopsied patients with cancer of the breast as opposed to an incidence of 37.5 per cent in a control group. In a subsequent report McManus and Sommers[49] suggested that the therapeutic effects of castration for metastatic cancer of the breast in patients shown to have cortical stromal hyperplasia are better than they are in patients whose ovaries do not show cortical stromal hyperplasia.

Data from the Canton of Zurich, Switzerland,[50] where the death rate from thyroid cancer has decreased subsequent to the use of iodized salt, would suggest a similar relationship between thyroid neoplasia and goitrogenesis, presumably mediated via the pituitary, in the human being as has been demon-

strated in rats. In this canton, iodized salt was first introduced in 1923. Its use had gradually increased to 90 per cent by 1950. The incidence data for deaths from cancer of the thyroid per 100,000 for males and females were as follows: 1906-1915, 2.04 and 1.43; 1916-1925, 2.12 and 1.59; 1926-1935, 1.40 and 1.74; 1936-1945, 0.65 and 0.94. This marked decrease in cancer of the thyroid strongly suggests that prophylaxis of goiter is a prophylaxis against cancer of the thyroid. Presuming that goitrogenesis in human beings is mediated as in rats by the patient's increased production of TSH, we might suggest that TSH contributes to the genesis and growth of thyroid cancer.

Unfortunately, our techniques for demonstrating gonadal or pituitary hormones in blood or urine are still quite inadequate and we are unable to report on the metabolism of ovarian or pituitary hormones. However, the late Dr. Konrad Dobriner of the Sloan-Kettering Institute and Dr. Seymour Lieberman now of the College of Physicians and Surgeons[51, 52] have reported extensive studies on the urines of normal human beings and of patients with various neoplastic diseases. In these studies, they have concentrated on a separation of the various steroids in the urine. The major steroids isolated by them from the urines of normal men and women were androsterone, etiocholanolone, 11-hydroxyandrosterone, and 11-keto-etiocholanolone. In the urine of patients having a variety of cancers, they demonstrated another steroid which they very seldom have found in normal human beings, 11-hydroxyetiocholanolone. This steroid, because of its structure, is thought to be a metabolite of one of the adrenal steroids, normal or abnormal. It is not yet known what role this steroid plays in the normal or morbid body economy of these patients. It is hoped that studies now in progress may throw light on this question.

Experimentally Induced Hormonal Control of Human Cancer

A third approach to this problem is found in the clinical experiments in which attempts have been made to affect the course of certain human cancers by altering the hormonal environment.

The sequence of events which led to the endocrinologic studies in patients with metastatic carcinoma of the prostate is one of the most fascinating accounts in experimental medicine. In 1936, the Gutmans[53] of the College of Physicians and Surgeons reported that they had found a high titer of phosphatase in the metastasis of a patient who had carcinoma of the prostate, which reacted only at an acid pH level. Subsequent studies by the Gutmans[54] and by Woodard[55] demonstrated an elevated acid phosphatase level in the blood of patients with metastatic cancer of the prostate. The Gutmans[56] then demonstrated that this enzyme is present in normal prostates and that it could be increased in the prostates of monkeys by administering testosterone.[57]

Studies done by Huggins and associates[58, 59] at about the same time demonstrated that prostatic secretion in dogs was decreased by castration. They also demonstrated that the administration of testosterone caused a regeneration of the prostate and that this could be inhibited by the administration of estrogens.

Huggins, Hodges, and Stevens[60, 61] then applied these physiologic considerations in the treatment of patients with metastatic cancer of the prostate. They castrated 21 such patients and observed an appreciable clinical improvement in 15 patients. There was a fall in the serum acid phosphatase in all but 2 cases. There was an increase in body weight and an increase in the hemoglobin levels. Shrinkage of the primary lesions was also observed. They also reported that the administration of testosterone to such patients resulted in an increase in the serum acid phosphatase whereas the administration of estrogenic hormones caused a fall in the blood levels of this enzyme.

These observations by Huggins have been widely confirmed during the past decade. An analysis of pooled cases, from 14 clinics, which had received endocrine treatment, has recently been published by Nesbit and Baum.[62] Of 115 patients with and without metastases on admission treated with diethylstilbestrol, only 18.3 per cent survived 5 years. Only 9 per cent of 504 untreated patients followed between 1925 and 1940 survived for 5 years.

In 1945 Huggins and Scott,[63] who reasoned that relapses in patients who had made favorable responses following castration were due to androgens being elaborated by the adrenal, did bilateral adrenalectomies in 4 previously castrated patients who had later relapsed. Three of these patients died of adrenal insufficiency in the postoperative period. In one patient who survived for more than three months they reported that there was relief of pain and even shrinkage of the primary tumor. The fact that cortisone has recently been available in adequate amounts has made it possible to expand studies on the effect of adrenalectomy in cancer of the prostate and other diseases. In 1952, Huggins and Bergenstal[64] reported their observations on seven patients with metastatic cancer of the prostate whose disease had relapsed following previous responses to antiandrogenic therapy. One patient died postoperatively. In four patients some of the following effects were observed: relief of intractable bone pain, gain in body weight, and a reduction in acid phosphatase. In two patients there was a significant shrinkage of large nodular prostates. In two patients no improvement whatsoever was observed.

From our own institution, West, Hollander, Whitmore, Randall, and Pearson[65] have reported the effect of adrenalectomy in 11 patients with advanced carcinoma of the prostate who had relapsed after previous response to castration and estrogen therapy. Transient relief of pain was observed in 10 of their patients. Shrinkage of tumor tissue was observed in 2 patients. The most recent results of these investigators in 17 patients are transient relief of pain in 15, and transient regression of tumors in 2 patients.

Notwithstanding the theory originally advanced by Huggins that the benefit of castration and now of adrenalectomy in these patients is due to removal of the body's two major sources of testosterone and other androgens, it has been demonstrated by Brendler, Chase, and Scott[66] and by Hollander and Whitmore[67] that the administration of testosterone is followed by exacerbation of the disease in only a fraction of the cases. Hollander and Whitmore[67] have observed in 24 patients with metastatic prostatic cancer that testosterone caused a rise in acid

phosphatase in only 9 cases and an increase in symptoms in only 5 cases. It would appear then that we may have to look for some other mechanism with which to explain these well-established therapeutic effects of castration in prostatic cancer. Indeed, Dr. C. D. West[68] who has been studying the spermatic vein blood of dogs and human beings for steroidal substances has already isolated from dogs' testicular blood in addition to testosterone $\triangle^4$ -androstenedione 3, 17. Further studies of such bloods may result in the isolation of even more hormonal compounds which might play a role in the genesis of prostatic cancer.

It was stated earlier that Schinzinger,[5] a German surgeon, was the first to suggest castration for cancer of the breast. Beatson,[6] a surgeon from Glasgow, reported in 1896 having castrated two young women with advanced metastatic cancer of the breast. He reported relief of pain and regression of the cancerous growths in these patients. Following Beatson's report, there were numerous reports of this type of treatment for mammary cancer. Then, for nearly 25 years, there was no activity in this field. Between 1921 and 1930 several writers recommended roentgen castration of premenopausal women with cancer of the breast. In 1938, Dresser[69] reported on a series of 57 patients whose ovaries he had attempted to destroy with x-ray. He reported beneficial effects in 30 per cent of his cases. In 1945, Adair, Treves, Farrow and Scharnagel[70] reported observations on 335 women with advanced carcinoma of the breast, whom they had castrated, 304 by x-ray and 31 surgically. In this group they observed objective benefit in only 15 per cent. They concluded that castration in general exerts only a temporarily beneficial effect. In cases which are improved, the growth process appears to be retarded for about two years. They also reported that castration in 8 males with advanced carcinoma of the breast resulted in spectacular regressions of the disease. In 1948, Treves[71] reported the results of castration in 13 male patients with advanced carcinoma of the breast. The results in this group were just as spectacular as in the previous series with regression of local lesions and healing of skeletal metastases.

Recently Pearson, West, Hollander, and Treves[72] of the Sloan-Kettering Institute have devised an objective method of measuring the rate of growth in bone of osteolytic metastases from breast cancer. The theoretical considerations for this procedure are presented in tabular form. A normal individual on a low-calcium diet (200 mg. per day) excretes 50 mg. of calcium per day in the urine, 200 mg. in the feces, and is in negative calcium balance by 50 mg. If it is assumed that the growth of 1 gram of tumor tissue destroys 1 gram of bone, then 100 mg. of calcium should be excreted since this is the approximate calcium content of one gram of bone. Nearly all of this calcium is excreted in the urine. Thus on a 200 mg. daily intake of calcium in a patient whose bony metastases are growing at the rate of 1 gram per day the patient would be excreting 150 mg. of calcium in the urine each day, and would have a calcium deficit of 150 mg. If the tumor is destroying more than 5 grams daily of bone the urinary calcium will exceed 500 mg. daily and a hypercalcemia may develop.

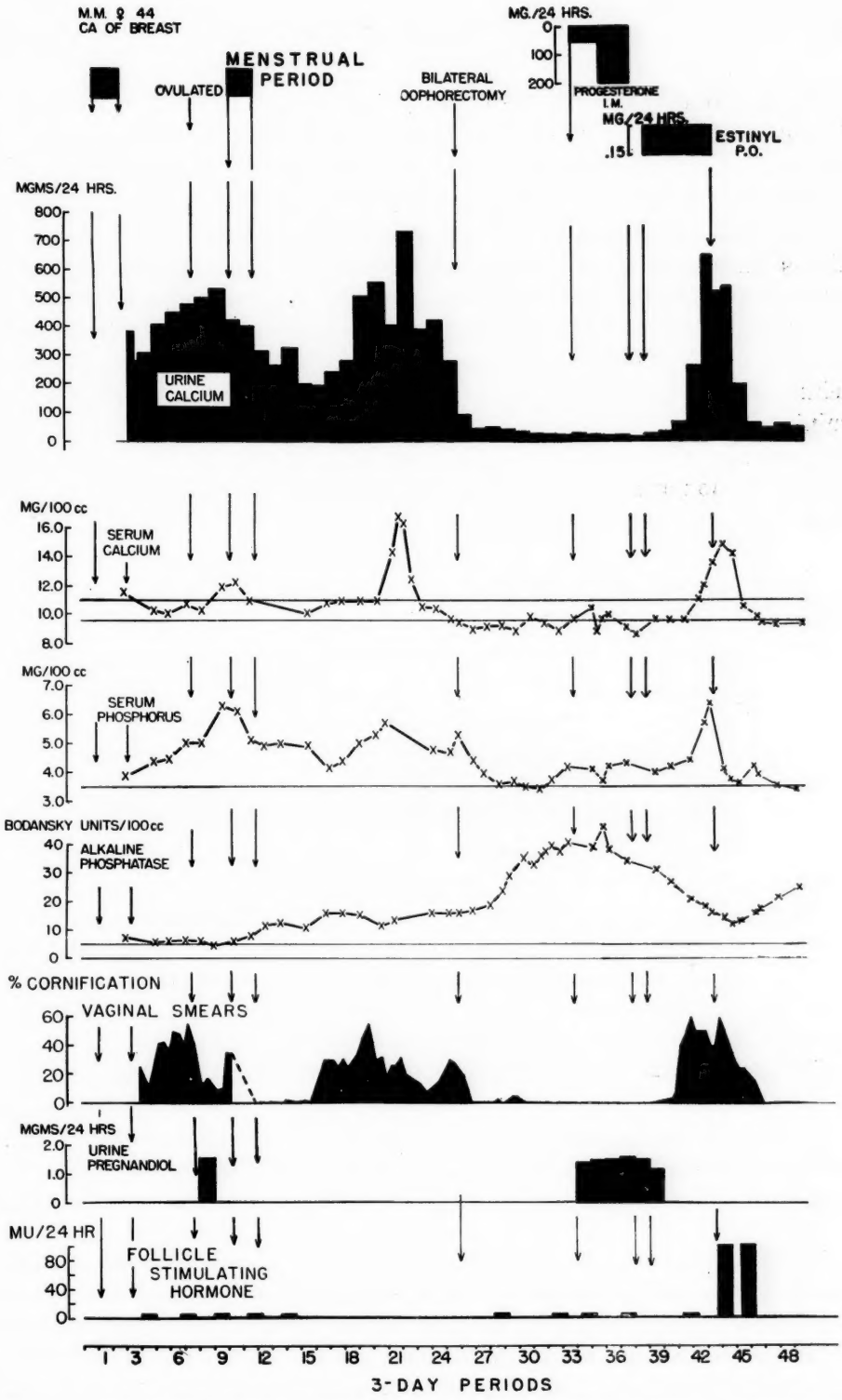

Fig. 1.—The urinary calcium excretion in a patient with osteolytic metastases from carcinoma of the breast, as affected by the menstrual cycle, castration, progesterone, and estrogens.

It is to be noted that the urinary calcium though high was lowest immediately after a menstrual period and highest just prior to menstruation. Immediately following castration the urinary calcium fell to normal levels and was not affected by the administration of progesterone. The administration of estrogens caused a prompt increase in urinary calcium. It is to be noted that hypercalcemia did not occur until after the daily urinary calcium reached levels of 500 mg. or more.

By applying these considerations in following a group of premenopausal patients having cancer of the breast with osteolytic metastases, Pearson and associates[72] have observed that patients whose disease is benefited by castration have cyclic patterns in the urinary calcium levels. Those patients who have not had cyclic patterns have failed to respond to castration. In those patients whose urinary calcium levels returned to normal following castration they have studied the effects of progesterone and of estrogens. Progesterone was found to have no effect on tumor growth. Estrogens in physiologic doses, however, have been observed to cause a marked and rapid increase in urinary calcium and in the serum calcium, which regressed promptly after stopping administration of the estrogenic hormone (Figs. 1 and 2). Thus we have a demonstration that estrogens will stimulate growth of the breast cancer. Thus far we do not have proof that estrogens cause breast cancer in the human being.

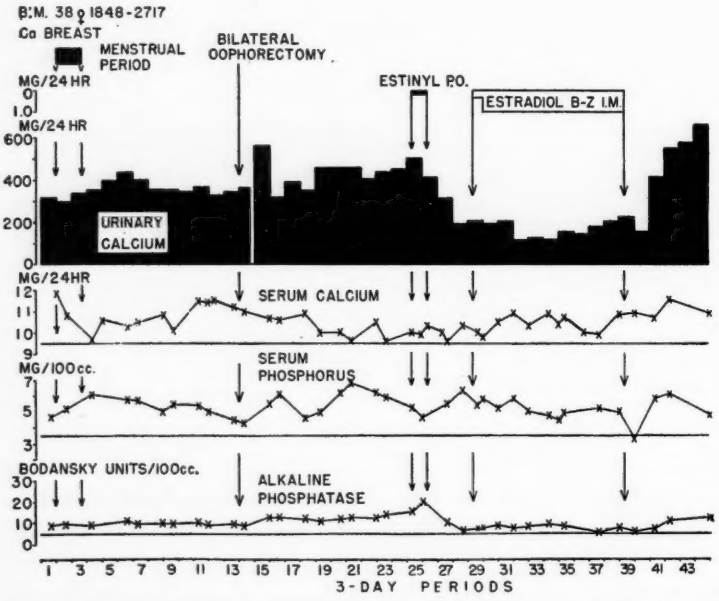

Fig. 2.—The urinary calcium excretion in a patient with osteolytic metastases from carcinoma of the breast who did not respond to oophorectomy.

It is to be noted that there was no significant change following menstruation, castration. The administration of estrogens was followed by a decrease in urinary calcium.

In 1939, Nathanson and Andervont[73] reported that prolonged administration of testosterone to female mice of a high mammary cancer strain resulted in a significant decrease in the number of mammary tumors which ultimately developed. Following this report, there appeared reports by Farrow and Woodard[74] and by Fels[75] on the treatment of metastatic cancer of the breast with testosterone. The former workers reported symptomatic improvement without objective evidence of benefit. The latter investigator reported improvement in one patient with regression in soft-tissue and bony metastases. Notwithstanding the unspectacular results in some of the earlier reports,

continued studies have resulted in greater understanding and significant therapeutic results in patients with metastatic cancer of the breast treated with testosterone.

In 1944, Haddow and associates[76] first described the use of synthetic estrogens in the treatment of carcinoma of the breast and of other sites. In this country, Nathanson[77] was the first to demonstrate a therapeutic effect of estrogens in postmenopausal women with advanced mammary carcinoma. During the past eight years, several clinics have been actively studying the therapeutic effects of androgenic and estrogenic hormones on human mammary cancer.

The policy has been to administer testosterone propionate intramuscularly in doses of 50 to 100 mg. three times a week to menstruating or early postmenopausal patients. Estrogens are administered orally as ethinyl estradiol, 1 mg. three times daily, or diethylstilbestrol, 5 mg. three times daily, to women who are 10 or more years postmenopausal.

The results of such therapeutic programs in the breast clinic of Memorial Center[78] are as follows: In the testosterone-treated patients: recalcification of osteolytic lesions has been observed in 19 per cent of 133 patients having osseous metastases. In 174 patients with soft-tissue disease, improvement, i.e., significant and measurable decrease in the size of palpable lesions and healing of ulcers has been observed in 22 per cent. A decrease in the size of pulmonary nodules has been observed in only 2 of 48 cases. In the estrogen series, 28 per cent of 36 cases of osseous disease have shown recalcification of one or more lesions, 41 per cent of 111 cases had significant improvement in the soft-tissue sites of disease, and 33 per cent of 39 cases of pulmonary disease have shown shrinkage of the pulmonary metastatic nodules. Although there is considerable variability in the rate of response, most successfully treated cases demonstrate improvement within three months.

Therapy with testosterone often leads to troublesome virilization, hirsutism, deepening of the voice, acne, increased libido, and clitoral hypertrophy. It may also be complicated by sodium and water retention necessitating diuretic measures.

Recently Huggins and Yuan Dao[79, 80] have reported their observations in patients who had been adrenalectomized for advanced mammary cancer. In their most recent publication they report on 53 women with advanced cancer of the breast in whom they had done total adrenalectomies. In 25 cases, the adrenalectomy was combined with oophorectomy. In these patients we cannot evaluate the effect of adrenalectomy. Of twenty-five patients who survived adrenalectomy alone 10 were reported to have shown regression of the disease "of some magnitude." They also reported on two previously castrated males with carcinoma of the breast whom they subjected to adrenalectomy. In one there was regression of pulmonary metastases but progression of cerebral metastases shortly after adrenalectomy.

West and co-workers[65] have reported their studies on the effect of adrenalectomy in 9 patients with advanced carcinoma of the breast, who had

previously been treated by castration and steroids but either had failed to respond to such treatment or had relapsed following initial responses. Objective evidence of improvement was observed in 3 cases. There was shrinkage of soft-tissue disease and evidence of improvement in skeletal lesions (Fig. 3). At the present time they have 23 patients with carcinoma of the breast in whom they have evaluated this procedure. Objective improvement has been observed in 9 patients. The improvement, though striking, is usually only transient. However, it has been great enough to warrant further investigation for at least a better understanding of the mechanism involved in those patients who do respond to this procedure.

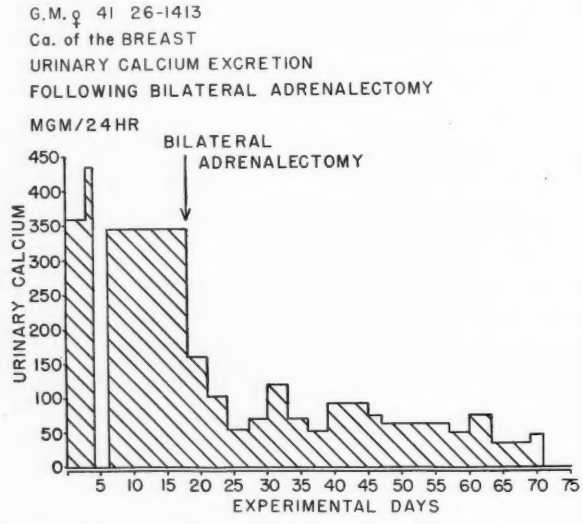

Fig. 3.—The effect of bilateral adrenalectomy on the urinary excretion of calcium in a patient with osteolytic metastases, who had previously responded to castration.

It might seem to be paradoxical, but beneficial effects have also been obtained from the administration of cortisone or of ACTH in patients with certain types of tumors. It was first demonstrated by Murphy and Sturm[81] and then by Heilman and Kendall[82] that the administration of Kendall's Compound E (now known as cortisone) to mice bearing lymphosarcomas resulted in a shrinkage of the tumors. Pearson and Eliel[83] reported in 1949 that the administration of cortisone or of ACTH to patients with certain lymphomatous diseases resulted in a spectacular shrinkage of the tumor masses with metabolic changes which reflected the rate and amount of tumor destruction. Cessation of hormone administration is followed by prompt recurrence of the tumors. Subsequent studies have revealed that some patients with lymphosarcoma, chronic lymphatic leukemia, or multiple myeloma can be successfully treated repeatedly with either of these hormones or with 11-hydroxycortisone (Compound F). It has also been demonstrated[84] that patients with these diseases can be carried on cortisone for prolonged periods of time and that the disease is held under control by such treatment if dosage of the hormone is adequate.

The same investigative group has also explored the therapeutic effects of these hormones in acute leukemia and other neoplasms.[83, 85] They observed that acute leukemia responds once or twice to such an altered hormonal environment.

Recently Pearson and co-workers[72] have demonstrated in 3 patients whose breast cancers were not influenced by castration that the administration of cortisone in pharmacologic doses had an inhibitory effect on the growth of osteolytic skeletal metastases (Fig. 4). The mechanisms by which these inhibitory effects of the adrenal steroids are exhibited on various tumors remain unexplained.

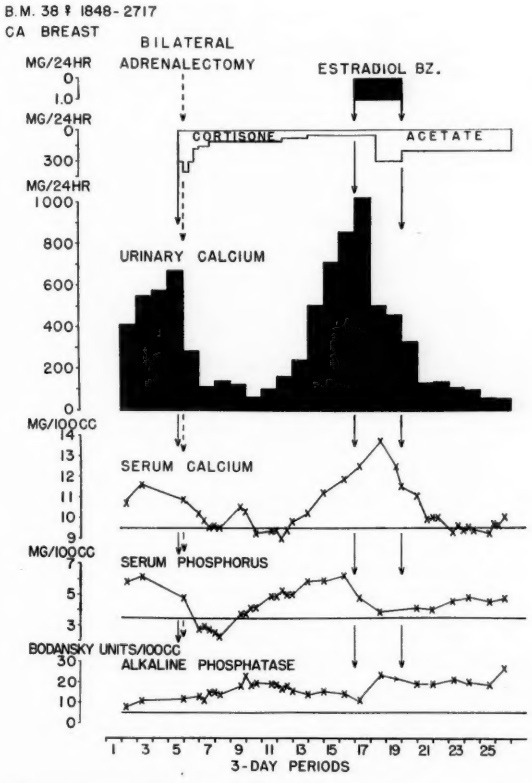

Fig. 4.—The effect of cortisone on the urinary excretion of calcium in a patient with osteolytic metastases from a cancer of the breast.

Following adrenalectomy there was a decrease in urinary calcium which increased again after decreasing the large postadrenalectomy doses of cortisone. Following the reinstitution of large doses of cortisone the urinary calcium again fell to normal.

Recent studies have also demonstrated that many cancers of the thyroid can very effectively be brought under control of certain physiologic mechanisms. Indeed, a large percentage of metastatic tumors of the thyroid has been forced to function much as normal thyroid tissue does. Although it has been demonstrated[86] that in 100 cancers of the thyroid 46 possessed the capacity to concentrate radioactive iodine, none of these tumors was capable of concentrating any more than a fraction of the iodine trapped by normal thyroid tissue. However, in one-half of a group of 52 patients with metastatic cancer

of the thyroid, it has been demonstrated[87] that ablation of the normal thyroid results in previously nonfunctioning metastatic lesions assuming the function of normal thyroid tissue, i.e., concentrating radioactive iodine, and even maintaining the patient in a euthyroid state. It has also been demonstrated that the administration of thyrotrophic hormone will induce function in the tumors of about one-third of the cases studied. Finally, it has been demonstrated in 62 per cent of a series of 42 previously totally thyroidectomized patients having skeletal or pulmonary metastases that the prolonged administration of thiouracil or of tapazol, agents which augment the action of thyrotrophic hormone, results in the metastatic lesions acquiring maximum capacity to concentrate radioactive iodine (Fig. 5). From the practical point of view, this has permitted us to administer radioactive iodine in therapeutic amounts which have had a demonstrable cancerocidal effect.

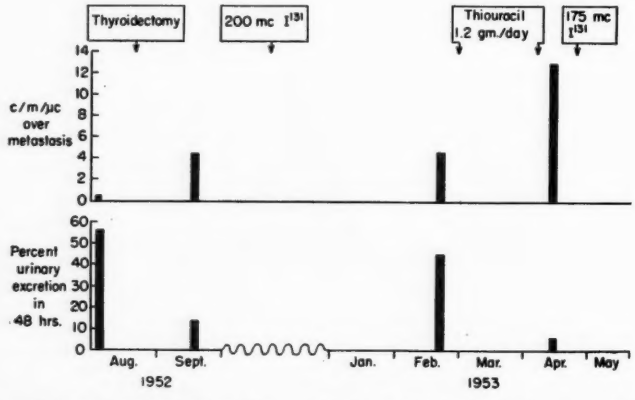

Fig. 5.—The uptake of radioiodine by a single metastatic lesion, and the urinary excretion of radioiodine following thyroidectomy and after treatment with thiouracil.

With the evidence presented this evening, I believe we can now say that several cancers can be made to respond to certain physiologic stimuli. In some instances tumors have been induced by pharmacophysiologic hormonal stimuli. In others the growth or function of certain cancers has been altered by changing the hormonal environment. Thus I believe that we are justified in challenging the concept that cancer is autonomous.

Although none of the endocrine treatments of cancer discussed this evening have been demonstrated to have lasting curative effects, I believe that these considerations on the hormonal influences on cancer can be considered as major and important steps toward ultimate understanding and rational treatments of these diseases.

Summary

It has been demonstrated in various laboratories that the administration of estrogenic hormones to experimental animals results in the production of tumors of the following tissues: breast, cervix, uterus, testes, and lymph nodes. It has also been demonstrated that the administration of pituitary

hormones or the induction of increased elaboration of certain pituitary hormones results in the development of uterine placentomas, ovarian, lymphatic, lung, adrenal, breast, testicular, and thyroid tumors.

It has been amply demonstrated that by altering the hormonal environment the following human tumors can be made to recede or to function like normal tissues, prostate, breast (male and female), lymphatic, and thyroid. These observations are being further investigated for clues which may ultimately lead to physiologic methods of controlling the development and course of such tumors.

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CEREBRAL CIRCULATION AND METABOLISM IN TOXEMIA OF PREGNANCY. OBSERVATIONS ON THE EFFECTS OF VERATRUM VIRIDE AND APRESOLINE (1-HYDRAZINOPHTHALAZINE)*

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ATTEMPTS to understand the functionings of the brain in man have been so unfruitful that our present concepts of cerebral function are based much more upon speculative theory than on scientific fact. This has been especially true of the cerebral symptoms of pregnancy toxemia. While many theories have been formulated as to the cause of convulsions and coma in this disease, that of Rosenstein,[1] postulating the presence of cerebral ischemia, and that of Halbertsma,[2] assuming deficient cerebral oxidation, though they originated during the last century, have been most widely accepted, and still form the nucleus of thought concerning this problem.

Excellent pathologic studies[3-11] and the electroencephalogram[12, 13, 14] have added measurably to our knowledge, but progress in the understanding of cerebral function in toxemia of pregnancy has been hindered by the lack of methods with which to study the dynamics of the internal environment of the brain during the active course of the disease. A definite advance was made, however, when Kety and Schmidt of the Department of Pharmacology of the University of Pennsylvania devised the nitrous oxide method for the quantitative measurement of cerebral blood flow.[15]

Method

The nitrous oxide method has been well described in the recent literature.[16] It involves the simultaneous withdrawal of venous blood from the internal jugular bulb and arterial blood from the femoral artery over a period of ten minutes while the patient is breathing a mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen. Mean arterial blood pressure is measured directly from the femoral artery with a damped mercury manometer. Blood gas analyses of nitrous oxide, oxygen, and carbon dioxide are made with the Van Slyke-Neill apparatus.

As previously described,[17] cerebral blood flow (CBF) is measured in cubic centimeters per 100 Gm. of brain per minute. Cerebral oxygen metabolism ($CMRo_2$)† may then be calculated in cubic centimeters of oxygen utilized per 100 Gm. of brain per minute, and cerebral vascular resistance (CVR)‡ in millimeters of mercury pressure per cubic centimeter of blood

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†$CMRo_2 = CBF \times \frac{(A\text{-}V)o_2}{100}$

‡$CVR = \frac{MABP}{CBF}$

flow per 100 Gm. of brain per minute. The respiratory quotient (RQ) is calculated by computing the relationship between the oxygen uptake by the brain and the amount of carbon dioxide given off.*

It appeared that such a method offered an unparalleled opportunity to study some of the most basic functions of the brain in toxemia of pregnancy. During the past six years approximately 600 cerebral blood flow investigations have been carried out upon 325 pregnant women. The aims of this investigation were threefold:

First, to ascertain normal values in uncomplicated pregnancy and to compare them with those of nonpregnant individuals;

Second, to establish the values for the several types of toxemia of pregnancy: (a) pre-eclampsia, (b) essential hypertension with superimposed acute toxemia, (c) eclampsia;

Third, to determine the effects upon the brain of various drugs and therapies used symptomatically in this disease of obscure causation, with the hope of gaining new insight into the pharmacologic response of this organ in toxemia, and of establishing a more logical approach to therapy.

The first two objectives have been accomplished.[17, 18]

First Objective.—The results in normal pregnancy (average of 105 patients) are shown and compared with results in nonpregnant individuals in Table I. The important functions of cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance, and respiratory quotient are almost identical in normally pregnant and nonpregnant persons. However, in normally pregnant women the arterial and venous concentrations of oxygen and carbon dioxide are much lower. This is apparently due to the so-called hydremia of pregnancy with relative increase of plasma volume and lowered hemoglobin concentration. Thus, with normal oxygen saturation, the arterial oxygen content is 26 per cent lower in late pregnancy. This finding is compatible with the degree of plasma increase shown by others.[19] This in no way interferes with the oxygen utilization by the brain as shown by normal A-Vo_2 and $CMRo_2$ values.

TABLE I. COMPARISON OF CEREBRAL FUNCTION AND BLOOD GASES IN NORMAL PREGNANT AND NORMAL NONPREGNANT INDIVIDUALS

	NONPREGNANT	PREGNANT	UNITS
Mean arterial blood pressure	86	84	mm. Hg
Cerebral blood flow	54	54	c.c./100 Gm. Brain/min.
Cerebral oxygen metabolism	3.3	3.5	c.c./100 Gm. Brain/min.
Cerebral vascular resistance	1.6	1.6	mm. Hg c.c./100 Gm. Brain/min.
Respiratory quotient	0.99	0.96	—
Arterial oxygen	18.0	14.3	Vol. %
Arterial carbon dioxide	49.0	39.6	Vol. %
Venous oxygen	11.7	7.9	Vol. %
Venous carbon dioxide	55.0	45.8	Vol. %
A-Vo_2	6.3	6.4	Vol. %

Second Objective.—Table II shows the effects of the various types of toxemia on the brain. Cerebral blood flow is not affected by this disease, refuting the theories of Traube and Rosenstein[1] and of Zangemeister[20] that there is a generalized diminishing of the brain's blood supply. It should be pointed out, however, that the method used actually measures the over-all cerebral blood flow, and does not give information concerning isolated areas of the

*$RQ = \frac{(V\text{-}A)Co_2}{(A\text{-}V)o_2}$

brain. Cerebral oxygen metabolism is normal in nonconvulsive toxemia, but is significantly depressed during the coma of eclampsia. This lowered oxygen consumption is present, even though the arterial oxygen supply to the brain is normal, suggesting a histotoxic anoxia. The cerebral vascular resistance is significantly increased in both convulsive and nonconvulsive toxemia. This adds to the evidence that toxemia of pregnancy is associated with a generalized vasospasm.[21, 22] The respiratory quotient does not deviate notably from unity, emphasizing that the brain utilizes carbohydrates almost exclusively as a source of energy and that toxemia of pregnancy does not alter this metabolism.

TABLE II. THE EFFECTS OF THE TOXEMIAS OF PREGNANCY ON CEREBRAL FUNCTION*

NO. OF PATIENTS	DIAGNOSIS	MABP MM. Hg	CBF C.C./100 GM. BRAIN/MIN.	$CMRO_2$ C.C./100 GM. BRAIN/MIN.	CVR MM. Hg C.C./100 GM. BRAIN/MIN.	RQ
105	Normal pregnancy	84	54	3.5	1.6	0.96
76	Hypertensive toxemia	129†	53	3.3	2.6†	0.98
83	Pre-eclampsia	119†	55	3.4	2.2†	0.95
8	Eclampsia	124†	51	2.8†	2.5†	1.06

*MABP = Mean arterial blood pressure.
CBF = Cerebral blood flow.
$CMRO_2$ = Cerebral oxygen metabolic rate.
CVR = Cerebral vascular resistance.
RQ = Respiratory quotient.
†Statistically significant change from normal values.

Third Objective.—Our third aim, the project of studying the effects of therapy on the brain, has developed along two lines. One has been the evaluation of the sedatives commonly employed in this condition, because of the depression of cerebral oxygen metabolism already existent in the most severe stage of the disease. The other has been the study of various types of vasodilators, for the relief of the increased cerebral vascular resistance present in all types of toxemia of pregnancy. Several drugs have been investigated in both of these groups.[23-27] This study is concerned with two drugs in the latter category; one a very old one, *Veratrum viride;* and the other a new one, Apresoline (1-Hydrazinophthalazine).

Material

Eighty-four investigations were carried out on 42 women in the latter weeks of pregnancy or the early puerperium; 24 were patients in the third trimester with toxemia of pregnancy, 14 having pre-eclampsia per se, and 10 having acute toxemia superimposed on mild essential hypertension. The remaining 18 were normally pregnant women and were equally divided in the evaluation of the two drugs. No therapy was allowed for at least 12 hours before the control investigation (c). Immediately after the first blood flow determination the drug being studied was administered, and the second observation (e) was carried out as soon as the maximum effect of the drug was attained.

Observations on Veratrum Viride

Veratrum viride, for over a century a substance of great controversy, has been recently subjected to careful scientific investigation, and is proposed by some as an acceptable hypotensive agent in the treatment of toxemia of pregnancy and essential hypertension. It was introduced to obstetrics by

Fordyce Barker,[28] who, in 1850, used it in the therapy of puerperal fever. It was first utilized in eclampsia by Baker[29] of Eufaula, Alabama, in 1859. Thereafter *Veratrum viride* was widely used in the therapy of severe toxemia,[30-35] being challenged in popularity only by bloodletting. The scholarly articles by Jewett[36] in 1887 and by Reamy[37] in 1895 before the American Gynecological Society had much to do with tipping the balance in favor of *Veratrum viride* and the gradual disappearance of the use of venipuncture in this disease.

TABLE III. EFFECTS OF VERATRUM VIRIDE ON BLOOD GASES

PATIENT	DIAGNOSIS	(A-V) O_2 (VOL. %)		(V-A) CO_2 (VOL. %)		ARTERIAL O_2 CONTENT (VOL. %)		ARTERIAL CO_2 CONTENT (VOL. %)		INTERNAL JUGULAR O_2 CONTENT (VOL. %)		INTERNAL JUGULAR CO_2 CONTENT (VOL. %)	
		C*	E*	C	E	C	E	C	E	C	E	C	E
R. H.	Normal	6.4	6.4	6.5	6.5	14.2	14.3	42.5	42.7	7.8	7.9	49.0	49.2
B. C.	Normal	6.3	6.3	6.3	6.3	14.2	14.2	43.6	43.6	7.9	7.9	49.9	49.9
B. J.	Normal	6.6	6.6	6.6	6.6	14.5	14.5	44.4	44.3	7.9	7.9	51.0	50.9
M. J.	Normal	6.2	6.2	6.2	6.2	14.9	14.9	39.2	39.2	8.7	8.7	45.4	45.4
D. V.	Normal	6.1	6.2	6.1	6.2	13.0	13.2	40.1	40.2	6.9	7.0	46.2	46.4
A. B.	Normal	6.3	6.3	6.3	6.3	15.0	15.0	38.3	38.3	8.7	8.7	44.6	44.6
M. S.	Normal	6.2	6.2	6.2	6.2	13.5	13.7	40.2	40.2	7.3	7.5	46.4	46.4
M. W.	Normal	6.7	6.6	6.6	6.6	16.4	16.4	41.2	41.2	9.7	9.8	47.8	47.8
A. B.	Normal	6.5	6.5	6.5	6.5	16.8	16.7	41.4	41.2	10.3	10.2	47.9	47.9
A. P.	Pre-eclampsia	7.0	7.0	7.3	7.2	15.6	15.6	36.0	36.1	8.6	8.6	43.3	43.3
C. B.	Pre-eclampsia	6.9	7.0	7.2	7.2	14.6	14.6	43.4	43.5	7.7	7.6	50.6	50.7
J. B.	Hypertensive	6.3	6.4	6.5	6.5	15.8	15.9	41.2	41.2	9.5	9.5	47.7	47.7
J. B.	Pre-eclampsia	6.2	6.3	6.3	6.3	12.8	12.8	42.2	42.3	6.6	6.5	48.5	48.6
C. H.	Hypertensive	6.2	6.3	6.2	6.3	15.2	15.3	42.6	42.9	9.0	9.0	48.8	49.2
E. T.	Hypertensive	6.2	6.2	6.1	6.2	14.1	14.1	39.8	39.8	7.9	7.9	45.9	46.0
A. C.	Pre-eclampsia	6.6	6.5	6.5	6.5	16.4	16.3	41.8	41.8	9.8	9.8	48.3	48.3
M. W.	Hypertensive	6.6	6.5	6.6	6.6	16.1	16.2	40.9	40.8	9.5	9.7	47.5	47.4
M. D.	Pre-eclampsia	6.5	6.5	6.5	6.5	16.0	16.2	40.9	40.7	9.5	9.7	47.4	47.2
L. F.	Hypertensive	6.3	6.3	6.3	6.3	11.9	12.1	39.6	39.6	5.6	5.8	45.9	45.9
Q. E.	Pre-eclampsia	6.4	6.4	6.4	6.5	16.9	17.1	47.8	47.8	10.5	10.7	54.2	54.3
	Mean values of normal patients	6.4	6.4	6.4	6.4	14.7	14.8	41.2	41.2	8.4	8.4	47.4	47.6
	Mean values of toxemic patients	6.5	6.5	6.5	6.6	15.0	15.1	41.5	41.5	8.6	8.6	48.0	48.0

*C = Control flow.
E = After medication.

While exceedingly popular at the turn of the century, *Veratrum viride* subsequently fell into disuse, partly because its dramatic effects were poorly understood and frequently attributed to an unphysiologic "cardiac depressant" action[32, 38] and partly because of the introduction of the Stroganoff and Dublin methods of therapy. There were, however, a few obstetric clinics which continued to use the drug in toxemia. This was notably so in the British Isles,[39, 40, 41] while in this country the Cincinnati General Hospital had for many years retained veratrum in its therapeutic regime for eclampsia. Reports from the latter institution by Bryant[42] in 1935, and Bryant and Fleming[43] in 1940 served as the stimulus which led to the revival of interest in this drug. The work of Willson,[44, 45, 46] of Craig and Jacobs,[47] and of Krayer and his associates[48, 49, 50] furnished basic knowledge, while the reports of

Irving[51] and of the Cincinnati group (Assali, Garber, and their associates)[52, 53, 54] have helped in the further clinical and scientific evaluation of the drug in toxemia.

TABLE IV. EFFECTS OF VERATRUM VIRIDE ON CEREBRAL FUNCTION*

PATIENT	DIAGNOSIS	MABP (MM. Hg)		CEREBRAL							
				CBF (C.C./100 GM. BRAIN/MIN.)		$CMRO_2$ (C.C./100 GM. BRAIN/MIN.)		CVR (MM. Hg/ C.C./100 GM. BRAIN/MIN.)		RQ	
		C	E	C	E	C	E	C	E	C	E
R. H.	Normal	82	72	50	43	3.2	2.8	1.6	1.7	1.0	1.0
B. C.	Normal	91	42	51	51	3.2	3.2	1.8	0.8	1.0	1.0
B. J.	Normal	106	70	43	52	2.8	3.4	2.4	1.3	1.0	1.0
M. J.	Normal	84	50	64	63	4.0	4.0	1.3	0.8	1.0	1.0
D. V.	Normal	71	43	56	62	3.4	3.8	1.3	0.7	1.0	1.0
A. B.	Normal	82	70	57	65	3.6	4.1	1.4	1.1	1.0	1.0
M. S.	Normal	65	55	54	59	3.4	3.7	1.2	0.9	1.0	1.0
M. W.	Normal	87	57	55	60	3.7	3.9	1.6	1.0	1.0	1.0
A. B.	Normal	80	52	57	58	3.7	3.8	1.4	1.0	1.0	1.0
A. P.	Pre-eclampsia	122	74	60	61	4.2	4.3	2.0	1.2	1.0	1.0
C. B.	Pre-eclampsia	120	59	62	44	4.3	3.1	1.9	1.3	1.0	1.0
J. B.	Hypertensive	115	68	52	56	3.3	3.6	2.2	1.2	1.0	1.0
J. B.	Pre-eclampsia	110	48	58	59	3.6	3.7	1.9	0.8	1.0	1.0
C. H.	Hypertensive	156	22	49	57	3.1	3.6	3.4	0.4	1.0	1.0
E. T.	Hypertensive	146	54	47	60	2.9	3.7	3.1	0.9	1.0	1.0
A. C.	Pre-eclampsia	110	46	50	54	3.3	3.5	2.2	0.8	0.98	1.0
M. W.	Hypertensive	108	87	50	52	3.3	3.4	2.2	1.7	1.0	1.0
M. D.	Pre-eclampsia	150	104	50	50	3.3	3.3	3.0	2.1	1.0	1.0
L. F.	Hypertensive	121	28	55	55	3.5	3.5	2.2	0.5	1.0	1.0
Q. E.	Pre-eclampsia	113	82	54	62	3.5	4.0	2.1	1.3	1.0	1.0
	Mean values of normal patients	83	57‡	54	57	3.4	3.6	1.6	1.0†	1.0	1.0
	Mean values of toxemic patients	125	61‡	53	55	3.5	3.6	2.4	1.1‡	1.0	1.0

*MABP = Mean arterial blood pressure.
CBF = Cerebral blood flow.
$CMRO_2$ = Cerebral oxygen metabolic rate.
CVR = Cerebral vascular resistance.
RQ = Respiratory quotient.
C = Control flow.
E = After medication.
† = Statistically significant, $P < 0.01$.
‡ = Statistically significant, $P < 0.001$.

Twenty women were studied. Nine were normal prenatal patients in various stages of pregnancy, and 11 had toxemia of pregnancy. Upon completion of the base line blood flow study, 3 minims (0.2 ml.) of a preparation of *Veratrum viride** were slowly given intravenously to all the toxemic patients, and to all but 3 of the normal group. The latter were given but 2 minims (0.13 ml.), inasmuch as they weighed less than 100 pounds. The investigation was then repeated (e) an average of 32 minutes later. The interim between control and experimental flows varied from 20 minutes to 50 minutes.

*Veratrone (Parke, Davis & Company).

An emetic effect was usually noted within 5 to 10 minutes, but subsided within 15 minutes in every case. There was also a transitory restlessness which gave way to relative composure within the same period of time. Fetal heart tones were not adversely affected in the patients studied, and there were no complications caused by the administration of *Veratrum viride.*

Results.—

The blood gas determinations of oxygen and carbon dioxide in the femoral arterial and jugular venous blood are shown in Table III. These remained within normal limits following the administration of *Veratrum viride.*

Table IV depicts the data pertaining to mean arterial blood pressure, cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance, and respiratory quotient of the brain before and after *Veratrum viride* in both normal and pregnancy toxemia groups. Following *Veratrum viride* there was a significant fall in mean arterial blood pressure from 83 mm. Hg to 57 mm. Hg in normally pregnant women. This was accompanied by a diminished cerebral vascular resistance from the normal level of 1.6 mm. Hg per cubic centimeter per 100 Gm. of brain per minute, to a subnormal 1.0 mm. Hg. The respiratory quotient was undisturbed at unity, and the cerebral blood flow and the oxygen metabolism of the brain were essentially unaffected.

In pregnancy toxemia the mean arterial blood pressure was lowered from an average of 125 to 61 mm. Hg and the cerebral vascular resistance from 2.4 to 1.1 mm. Hg per cubic centimeter per 100 Gm. of brain per minute. These significant changes from abnormally high levels resulted in subnormal values almost identical with those obtained after the administration of *Veratrum viride* to normal pregnant patients. The respiratory quotient, cerebral blood flow, and oxygen metabolism were not notably affected.

Observations on Apresoline

During the past few years a number of new hypotensive substances have been synthesized. Among the most interesting is 1-Hydrazinophthalazine, first studied by the Swiss investigators Gross, Druey and Meier[55] and now being marketed under the name Apresoline.* The early studies of Grimson and Chittum,[56] of Reubi,[57, 58] and of Craver and Yonkman[59] corroborated the suggestion that this agent not only possessed hypotensive properties, but also exhibited a vasodilating effect upon the kidney with resultant increased renal blood flow. Being the only therapeutically acceptable substance with such an effect on the kidneys, combined with growing evidence that it neutralizes some of the known humoral vasopressor substances, Apresoline has recently become widely used in essential hypertension and to some degree in toxemia of pregnancy.

Thirteen toxemic patients and 9 normally pregnant women were given 40 mg. of Apresoline intramuscularly following the basic cerebral blood flow determination. The second investigation was then carried out an average of 35 minutes after administration of the drug, at which time the blood pressure was usually stabilized at its lowest level. With this dosage all patients were

*1-Hydrazinophthalazine, Ciba Pharmaceutical Products, Inc.

restless and apprehensive and complained of hot flushes and palpitation. Over one-half of the group experienced nausea, vomiting, and headache, while all exhibited tachycardia. The severity of these symptoms appeared to be related to the degree of hypotension brought about by the drug. The fetal heart tones remained normal in all cases, and no permanent ill effects due to the drug were encountered.

Results.—

The blood gas determinations of oxygen and carbon dioxide in both venous and arterial blood specimens are shown in Table V. These remained unaffected by the administration of Apresoline.

TABLE V. EFFECTS OF APRESOLINE ON BLOOD GASES

PATIENT	DIAGNOSIS	(A-V) O_2 (VOL. %)		(V-A) CO_2 (VOL. %)		ARTERIAL O_2 CONTENT (VOL. %)		ARTERIAL CO_2 CONTENT (VOL. %)		INTERNAL JUGULAR O_2 CONTENT (VOL. %)		INTERNAL JUGULAR CO_2 CONTENT (VOL. %)	
		C*	E*	C	E	C	E	C	E	C	E	C	E
M. W.	Normal	6.9	6.8	7.0	6.8	13.6	13.2	43.7	43.5	6.7	6.4	50.7	50.3
C. S.	Normal	6.2	6.4	6.5	6.5	13.0	13.4	35.8	36.2	6.8	7.0	42.3	42.7
M. D.	Normal	6.6	6.6	6.4	6.5	16.0	15.8	40.6	40.8	9.4	9.2	47.0	47.3
A. D.	Normal	6.3	6.4	6.5	6.5	14.6	14.9	42.4	42.8	8.3	8.5	48.9	49.3
C. S.	Normal	6.3	6.3	6.2	6.3	15.7	16.0	39.9	39.9	9.5	9.7	46.1	46.2
B. A.	Normal	6.3	6.4	6.6	6.6	12.7	13.0	43.4	43.7	6.4	6.6	50.0	50.3
E. K.	Normal	6.5	6.5	6.3	6.3	16.0	15.7	46.7	44.4	9.5	9.2	53.0	50.7
A. W.	Normal	6.3	6.4	6.4	6.4	16.2	16.0	46.1	45.9	9.9	9.6	52.5	52.3
L. F.	Normal	6.4	6.7	6.5	6.8	15.3	14.9	45.8	45.5	8.9	8.2	52.3	52.3
E. W.	Pre-eclampsia	6.3	6.4	6.5	6.5	13.9	14.2	41.6	42.1	7.6	7.8	48.1	48.6
M. B.	Pre-eclampsia	6.5	6.4	6.2	6.2	15.9	15.8	42.1	42.3	9.4	9.4	48.3	48.5
C. A.	Pre-eclampsia	6.5	6.5	6.5	6.5	11.9	11.5	37.3	38.0	5.4	5.0	43.8	44.5
J. M.	Hypertensive	6.8	6.8	6.8	6.8	15.0	15.3	43.4	44.2	8.2	8.5	50.2	51.0
M. H.	Hypertensive	6.7	6.7	6.9	6.8	16.2	16.0	49.5	49.0	9.5	9.3	51.4	55.8
R. R.	Hypertensive	6.3	6.3	6.1	6.1	14.6	14.3	40.7	40.8	8.3	8.0	46.8	46.9
M. T.	Pre-eclampsia	6.8	6.7	6.7	6.8	14.7	14.6	39.9	40.2	7.9	7.9	46.6	47.0
R. S.	Hypertensive	6.3	6.3	6.5	6.3	14.3	14.0	43.4	43.1	8.0	7.7	49.9	49.4
C. W.	Pre-eclampsia	6.3	6.3	6.2	6.2	13.9	14.0	44.5	44.8	7.6	7.7	50.7	51.0
R. B.	Pre-eclampsia	6.5	6.5	6.4	6.5	16.0	15.8	46.7	46.4	9.5	9.3	53.1	52.9
E. S.	Hypertensive	6.6	6.6	6.7	6.6	15.6	15.5	41.9	42.3	9.0	8.9	48.6	48.9
G. A.	Pre-eclampsia	6.4	6.4	6.4	6.4	16.0	16.2	48.4	48.5	9.6	9.8	54.8	54.9
M. R.	Pre-eclampsia	6.6	6.6	6.5	6.6	15.0	15.3	44.9	44.8	8.4	8.7	51.4	51.4
	Mean values of normal patients	6.4	6.5	6.5	6.5	14.8	14.8	42.7	42.5	8.4	8.3	49.2	49.0
	Mean values in toxemia	6.5	6.5	6.5	6.5	14.8	14.8	43.4	43.6	8.3	8.3	49.9	50.1

*C = Control flow.
E = After medication.

Table VI contains the data on mean arterial blood pressure, cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance and respiratory quotient of the brain before and after Apresoline, in both normal and toxemia of pregnancy groups. Following the administration of Apresoline to normally pregnant women, there was a fall in mean arterial blood pressure from 88 to 64 mm. Hg as well as a diminished cerebral vascular resistance from the normal level of 1.7 mm. Hg to a subnormal 1.1 mm. Hg per cubic centimeter per 100 Gm. of brain per minute. Cerebral blood flow was increased from

51 to 59 c.c. per 100 Gm. of brain per minute, while cerebral oxygen metabolism rose from 3.3 to 3.9 c.c. per 100 Gm. of brain per minute. The respiratory quotient was unaffected.

TABLE VI. EFFECTS OF APRESOLINE ON CEREBRAL FUNCTION*

PATIENT	DIAGNOSIS	MABP (MM. Hg)		CEREBRAL							
				CBF (C.C./100 GM. BRAIN/MIN.)		$CMRO_2$ (C.C./100 GM. BRAIN/MIN.)		CVR (MM. Hg/ C.C./100 GM. BRAIN/MIN.)		RQ	
		C*	E*	C	E	C	E	C	E	C	E
M. W.	Normal	95	80	52	57	3.6	3.9	1.8	1.4	1.01	1.0
C. S.	Normal	79	65	50	57	3.1	3.7	1.6	1.1	1.04	1.01
M. D.	Normal	82	72	53	64	3.5	4.2	1.5	1.1	0.97	0.98
A. D.	Normal	88	75	50	64	3.2	4.1	1.8	1.2	1.03	1.01
C. S.	Normal	95	52	52	61	3.3	3.8	1.8	0.9	0.98	1.0
B. A.	Normal	78	68	43	51	2.7	3.3	1.8	1.3	1.04	1.03
E. K.	Normal	98	76	53	61	3.5	4.0	1.9	1.2	0.99	0.97
A. W.	Normal	87	59	52	60	3.3	3.8	1.7	1.0	1.01	1.0
L. F.	Normal	87	33	50	60	3.2	4.0	1.7	0.6	1.01	1.01
E. W.	Pre-eclampsia	104	58	50	58	3.2	3.7	2.1	1.0	1.03	1.02
M. B.	Pre-eclampsia	132	35	53	60	3.5	3.8	2.5	0.6	0.95	0.97
C. A.	Pre-eclampsia	105	48	56	63	3.6	4.1	1.9	0.8	1.0	1.0
J. M.	Hypertensive	99	74	47	55	3.2	3.7	2.1	1.3	1.0	1.0
M. H.	Hypertensive	189	152	51	63	3.4	4.2	3.7	2.4	1.03	1.01
R. R.	Hypertensive	100	72	50	61	3.2	3.8	2.0	1.2	0.97	0.97
M. T.	Pre-eclampsia	120	84	51	55	3.5	3.7	2.4	1.5	0.98	1.01
R. S.	Hypertensive	142	59	67	71	4.2	4.5	2.1	0.8	1.03	1.0
C. W.	Pre-eclampsia	126	71	61	68	3.8	4.3	2.1	1.0	0.98	0.98
R. B.	Pre-eclampsia	117	60	56	66	3.6	4.3	2.1	0.9	0.98	1.0
E. S.	Hypertensive	163	138	58	65	3.8	4.3	2.8	2.1	1.02	1.0
G. A.	Pre-eclampsia	119	99	54	67	3.5	4.3	2.2	1.5	1.0	1.0
M. R.	Pre-eclampsia	123	42	57	65	3.8	4.3	2.2	0.6	0.98	1.0
	Mean values of normal patients	88	64†	51	59†	3.3	3.9†	1.7	1.1†	1.01	1.0
	Mean values of toxemic patients	126	76†	55	63†	3.6	4.1†	2.3	1.2†	1.0	1.0

*MABP = Mean arterial blood pressure.
CBF = Cerebral blood flow.
$CMRO_2$ = Cerebral oxygen metabolic rate.
CVR = Cerebral vascular resistance.
RQ = Respiratory quotient.
C = Control flow.
E = After medication.
† = Statistically significant, $P < 0.001$.

In the toxemic group there was definite lowering of mean arterial blood pressure from 126 to 76 mm. Hg and of cerebral vascular resistance from 2.3 to 1.2 mm. Hg per cubic centimeter per 100 Gm. of brain per minute. Cerebral blood flow was increased from 55 to 63 c.c. per 100 Gm. of brain per minute and cerebral oxygen metabolism from 3.6 to 4.1 c.c. per 100 Gm. of brain per minute. These changes were statistically significant. The respiratory quotient remained at unity.

Comment

Physiological Considerations.—

The brain has been referred to as a "powerful monarch" which through its nervous connections requisitions for itself from the rest of the body an

adequate and constant flow of blood at the expense, if necessary, of other organs.[60] Cerebral blood flow is regulated by two important factors, the systemic blood pressure and the degree of vascular resistance within the brain. Our studies strongly suggest that regulation of cerebral vascular resistance is of the greatest importance and it has been demonstrated that normal cerebral blood flow may be maintained by rapid variation of this resistance even though systemic blood pressure vacillates from hypertensive to normotensive or hypotensive levels. Although the influence of blood viscosity, brain edema, and spinal fluid pressure must be recognized, it is most probable that an augmented tone of the cerebral vessels is the major factor in determining the degree of increase of cerebral vascular resistance in toxemia of pregnancy. We have shown that all types of this disease are associated with such a change.[17] The cause for the increase in cerebral vascular tone in toxemia of pregnancy is unknown, but the answer must be associated with neurogenic, chemical, or humoral influences.

Nervous control of the cerebral vessels has not been well demonstrated[61] although sympathetic vasoconstrictor fibers[62] via the stellate ganglion and parasympathetic vasodilator fibers[63] via the geniculate ganglion have been shown to exist. Neurogenic activity over these pathways, perhaps mediated through a carotid sinus reflex,[64] has been suggested as a possible means utilized by the brain in its attempt to maintain blood flow within normal limits in the face of abnormal circumstances. However, there are two studies which supply evidence pointing away from neurogenic action as the main mechanism in this connection. First, it has been shown that bilateral stellate ganglion block[65] fails to bring about cerebral vasodilatation, leaving the impression that there is no vasoconstrictor tone being exercised through the cervical sympathetics. Second, it has been demonstrated that high spinal sympathetic block[66] given to patients with essential hypertension, with subsequent lowering of blood pressure, only partially relieved the increased cerebral vascular resistance present, so that cerebral blood flow and oxygen metabolism were compromised. Inasmuch as this does not occur after the administration of *Veratrum viride* or Apresoline, it is clear that these drugs do not depend alone upon neurogenic influences to adjust cerebral physiology, and that their hypotensive effects are not based on the peripheral pooling of blood associated with lowered cardiac output.

Among the most powerful means of affecting cerebral vascular tone is alteration of carbon dioxide and oxygen tensions or change in hydrogen ion concentration.[16] Schieve and Wilson[67] have pointed out that this tone is more closely related to arterial carbon dioxide than to pH in the absence of anoxia. Since in this study no significant changes occurred in the carbon dioxide or oxygen levels of either arterial or venous blood, it may be concluded that *Veratrum viride* and Apresoline do not make use of this means of affecting cerebral hemodynamics.

The possibility must therefore be strongly considered that some humoral agent may be the cause of the vasospasm of toxemia of pregnancy, and be

involved in the action of the hypotensive agents being studied. It has long been suspected that some such substance might be responsible for the vasoconstriction and increased arterial blood pressure in pre-eclampsia-eclampsia[68] as well as in essential hypertension.[69] Recently Taylor, Page, and Corcoran,[70] emphasizing Claude Bernard's belief that every organ has internal secreting properties, discovered that the cerebrum secretes a vasopressor substance upon the stimulation of visceral afferent nerve fibers. The same investigators[71] have also lately shown that the brain possesses a chemoreceptor system which has an important place in determining the response of the body to vasoactive substances.

Veratrum viride.—

The hypotensive effect of *Veratrum viride,* while not completely understood, is known to be mediated, at least partially, through the vagus, by direct stimulation of afferent nerve endings in the walls of the ventricles of the heart, bringing about depression of the vasoconstrictor center (von Bezold reflex).[72, 73] It also acts centrally on the brain's chemoreceptor system[71] and has a peripheral vasodilating action.[46] *Veratrum viride* exhibited a more pronounced hypotensive effect than Apresoline in both normal and toxemic patients. Normally pregnant women were affected to such a degree by *Veratrum viride* that their blood pressures were notably subnormal. This finding is in disagreement with the claim of Assali and his co-workers[74] that normally pregnant women are not significantly affected by veratrum. The lowering of arterial blood pressure per se was apparently not associated with the so-called "toxic symptoms" of nausea, vomiting, and excitation, inasmuch as the patient invariably became quieted after these transient signs, even though the blood pressure remained at low levels or continued to fall. It appears obvious that there is some depression of the central nervous system at this point, and this remarkable influence of veratrum, which was so impressive to the older clinicians,[28, 29, 32, 35] may well be, in itself, a factor militating against the development of convulsions.

Veratrum viride greatly decreased cerebral vascular resistance in both normal and toxemic groups. Humoral activity is suggested in the action of this drug not only by the fact that it inhibits cerebrotonin[75] but also because it exerts its effects even after medical block of the autonomic nervous system with benzodioxane, Priscoline, and tetraethylammonium chloride.[75] Whatever the medium through which *Veratrum viride* acts to bring about relaxation of spastic cerebral vessels, it does so without interfering with the vital physiology of the brain. Cerebral blood flow and oxygen metabolism are maintained even in the presence of a precipitous drop in blood pressure. A striking example of this is seen in the patient C. H. (Table IV), in whom the mean arterial blood pressure was reduced over 700 per cent from a level of 156 to 22 mm. Hg while cerebral blood flow and oxygen metabolism remained within normal limits. The marked relaxation of cerebral vasoconstriction brought about in this patient is evidenced by the fact that it took 3.4 mm. Hg pressure

before the drug was administered, and only 0.4 mm. Hg pressure afterward to force each cubic centimeter of blood through 100 Gm. of brain tissue in a minute's time. This maintenance of normality within the brain under the influence of *Veratrum viride* bears out the contention of others that this drug allows for remarkable homeostasis. Except for transient initial reductions, there is no interference with urinary output, renal blood flow, or hepatic-portal blood flow.[76] The ballistocardiogram[77] is improved and cardiac output remains normal in compensated hearts and is increased in patients with congestive heart failure. It has also been shown that the adaptive reflexes involving sympathetic vasoconstrictor responses are not inhibited, thus preventing postural hypotension or interference with variations in blood pressure that occur during normal activity.

Apresoline.—

Apresoline's site of action is unknown but the evidence is strong that it causes vasodilatation by reducing the outflow of sympathetic vasopressor impulses by central action.[78] It significantly lowered blood pressure in both the normal and toxemia groups. In contrast with veratrum, the lowering of blood pressure with Apresoline was associated with side reactions of nausea, vomiting, and apprehension. These symptoms seemed to increase as the blood pressure fell and continued until fairly normal levels were again attained. Apresoline decreased cerebral vascular resistance 48 per cent in toxemia and 35 per cent in normal pregnancy. The humoral activity of Apresoline is demonstrated by its neutralizing effects on cerebrotonin,[75] hypertensin, serotonin,[70] pherentasin[79] and norepinephrine.[80, 81, 82] Cerebral blood flow and cerebral oxygen metabolism were significantly increased with this drug. Whether or not these changes are desirable is unknown at the present time. The increased circulation of the brain is associated with a relatively greater lowering of cerebral vascular resistance than of mean arterial blood pressure. The marked increase in cardiac output[83] (over 100 per cent) brought about by Apresoline is probably a factor in this. These circulatory changes in the brain are similar to those caused by histamine,[84] probably accounting for the frequent severe headaches associated with Apresoline therapy which may be successfully treated by the administration of antihistaminic drugs. The reason for the increase in cerebral oxygen metabolism is not easily explained, although Wechsler and his associates[85] noted similar changes in anxiety states. All of the patients in this study were restless and apprehensive. This may be accounted for by the fact that larger doses of the drug were used by us. Hafkenschiel and his associates,[86] using smaller amounts of Apresoline, found no change in cerebral blood flow or oxygen metabolism in a group of hypertensive patients.

It seems that Apresoline does not bring about circulatory and metabolic compensation quite as gracefully as does *Veratrum viride*. This drug modifies the pressor response to the cold pressor test and produces postural hypoten-

sion.[87] It has the unique advantages, however, of increasing renal blood flow and coronary blood flow,[88] of improving the ballistocardiogram,[77] and of frequently augmenting urinary output while blood pressure falls.

It is hoped that these studies of cerebral circulation and metabolism may provide a steppingstone toward the ultimate understanding of the disturbed physiology of the brain and its rational treatment in toxemia of pregnancy.

Summary

1. Quantitative measurements of cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance, arteriovenous oxygen difference, mean arterial blood pressure, respiratory quotient of the brain, and blood gases have been reported and average values for the toxemias of pregnancy and normal pregnancy have been established.

2. Circulatory and metabolic functions of the brain have been studied before and after the administration of *Veratrum viride* and Apresoline in twenty-four patients with toxemia of pregnancy and eighteen normal pregnant women.

3. *Veratrum viride* significantly lowered the increased cerebral vascular resistance and mean arterial blood pressure present in toxemia of pregnancy, while cerebral blood flow, cerebral oxygen metabolism, respiratory quotient of the brain, and the blood gases remained normal.

4. Apresoline notably decreased mean arterial blood pressure and cerebral vascular resistance while bringing about increased cerebral blood flow and oxygen utilization by the brain. The respiratory quotient of the brain and the blood gases were unaltered.

5. Possible mechanisms of cerebral activity associated with toxemia of pregnancy have been discussed.

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Discussion

DR. CARL P. HUBER, Indianapolis, Ind.—The author of this scholarly investigation has presented a well-documented study of cerebral circulation in normal pregnancy and in pregnancy toxemia. It would appear that adequate control data have been a part of the investigation and that the number of patients in each group is sufficient to justify conclusions.

The information obtained from this study supports the increasingly accepted idea concerning the importance of vascular spasm as an essential factor in the development of the manifestations of pre-eclampsia and eclampsia. This would suggest that present attempts to control vascular spasm are, in the absence of more fundamental knowledge, the most satisfactory approach to the amelioration of the more damaging effects of the pregnancy toxemias.

It is justifiably emphasized that the drugs used in therapy are symptomatic treatment. The studies reported indicate, however, that there is a demonstrably logical basis for their administration. The author presents laboratory evidence in support of the claims based on clinical observation for the use of veratrum and the more recently employed Apresoline. Insufficient clinical observations are presented to demonstrate the superiority of these preparations in the end results of therapy of the toxemias. This does not necessarily detract from the importance of these observations.

Based upon the data reported, it seems logical that a combination of the two drugs studied might be more effective and perhaps safer than either drug used alone. It would be interesting to have the author comment, from his experience, upon any dangers inherent in the use of these preparations. It would also be interesting to have him comment upon the effects on cerebral circulation and metabolism of other preparations which are frequently used in the toxemic patient, such as the barbiturates, morphine, and magnesium sulfate.

It is to be pointed out that the technical procedures upon which this study is based are difficult of performance, and it is to be hoped that the data upon which conclusions have been based were as consistent as the tables presented seem to indicate.

DR. RUSSELL DE ALVAREZ, Seattle, Wash.—This newer investigation by Dr. McCall of cerebral blood flow, so clearly presented by him, opens another avenue of approach to the physiopathology of the toxemias of pregnancy. It permits the correlation of investigative results noted by him with those changes noted in the study of renal hemodynamics in the various toxemias of pregnancy.

While Dr. McCall has evaluated the effects of *Veratrum viride* and of Apresoline in the study of cerebral blood flow, we have studied these same drugs from the standpoint of

renal function in the same types of patients. Since we and others have reported the renal picture after the administration of *Veratrum viride,* I should like to attempt to correlate our findings in renal studies following the use of Apresoline.

Dr. McCall has found the cerebral blood flow to be uniformly and statistically significantly elevated following the use of Apresoline. However, these results cannot be interpreted as reflecting renal function in all types of toxemia. We have found Apresoline to act in one manner when administered to the pregnant essential hypertensive patient, but in quite a different fashion when applied in pre-eclampsia. The glomerular filtration rate is distinctly elevated over the control average following the administration of Apresoline in pre-eclampsia, particularly where a reduced glomerular filtration rate is operating, as it usually is in this condition. Among our group, in the essential hypertensive pregnant patient, on the other hand, the glomerular filtration rate is somewhat decreased, even in those cases where the control level was high.

The renal blood flow in pre-eclampsia is definitely increased after the administration of Apresoline, while a real decrease occurs in the pregnant patient with essential hypertension.

We have also noted an increased urinary output in the pre-eclamptic patient following Apresoline, but have noted no consistent change in the patient with essential hypertension. These findings in the urinary output apparently have not been related to the fall in blood pressure which uniformly occurs in all types of pregnancy toxemia, regardless of type. This would tend to suggest that the increase in urinary volume is dependent upon an increase or at least maintenance of the renal blood flow in pre-eclampsia.

Compatible with the findings of Dr. McCall, both types of patients have displayed an increase in extracellular fluid volume.

DR. J. HOFBAUER, Cincinnati, Ohio (by invitation).—Major efforts of recent date, such as the significant investigations of McCall, signalize the transition from supposition to reality. Our recent synthetic interpretation of the syndrome of toxemia in terms of disturbed homeostasis, as influenced by the heightened neuroendocrine activity of the pituitary-adrenal system (vasoexcitation) and the inadequacy of the vasodepressors (acetylcholine, monoamine oxidase) resulting from structural and functional damage of the liver, the placenta, and the capillary endothelium, keynoted the stellar part played by the physical equilibrium of the small vessels and their hyperreaction to Pitressin and noradrenalin in toxemia (Am. J. Surg., Oct., 1952). Relevant to the present discussion, the recent demonstration of both the elevation of efferent arteriolar resistance and higher sodium reabsorption as responses of the kidney to Adrenalin and noradrenalin (R. M. Berne: Am. J. Physiol. 171: 56, 1952), and the greatly increased splanchnic vascular resistance as a response to Pitressin highlights the fundamental importance of these endocrine products in toxemia (A. A. Lewis: J. Endocrinal., Jan., 1953).

The primary importance of hepatic function in maintaining normal balance of hormonal activity and neutralizing the pressor principles of the postpituitary and Adrenalin has been universally recognized. Hepatic function, however, has been found remarkably susceptible to nutritional deficiency (Biskind, Vitamins & Hormones 4: 147, 1946). The significant decrease of liver glycogen in toxemia, repeatedly emphasized in my preceding articles, assumes renewed interest in the light of recent evidence that Adrenalin causes breakdown of glycogen, decreases glucose utilization, and increases lactic acid formation (G. Halaas: J. Biol. Chem., 1950, p. 769).

Available data indicate that the monoamine oxidase activity of the liver and the placenta—important agents in the inactivation of noradrenalin—may be inhibited under anaerobic conditions and as the result of increased production of thyroxin. Depression of oxygen metabolism and higher titers of thyroxin are known to occur in toxemia. Recent evidence that morphine, like emotional stress, directly stimulates the neurohypophysis causing release of the antidiuretic hormone (Science, 1953, p. 225) renders the administration of this drug in eclampsia rather hazardous.

DR. McCALL (Closing).—Dr. de Alvarez asks where Apresoline acts in the brain. Our studies do not disclose this information. It has been suggested, however, that the rise in cerebral blood flow may be on the basis of increased cardiac output which is usually raised at least 100 per cent over normal with this drug.

Dr. de Alvarez has added greatly to our knowledge of renal physiology and pathophysiology in toxemia of pregnancy. It is important to correlate as closely as possible the studies on two such important organs as the brain and the kidney.

While the brain is only one of the organs which concerns us in toxemia, it is interesting to note that this organ, which itself represents only 2 per cent of the total body weight, uses almost 20 per cent of the heart's output of blood and consumes at least 20 per cent of the oxygen used by the entire body. The brain cannot store oxygen and, therefore, with its great demands, the least bit of disturbance may become very serious in a comparatively short period of time. This is what happens in eclampsia and is always imminent in pre-eclampsia. It is, therefore, most heartening to know that there are agents such as *Veratrum viride* and Apresoline which do not disturb cerebral homeostasis. Recently we have been using a mixture of Apresoline and *Veratrum viride.* We have done this in order to take advantage of the renal effects of Apresoline and the over-all excellent homeostatic effects of veratrum. It has been interesting to observe how well these patients with severe pre-eclampsia and eclampsia respond to such therapy. The urinary output has been consistently increased in the patients studied, even though they previously have had severe oliguria and have received adequate fluid.

As intimated by Dr. Huber, in some of our earlier work it was shown that cerebral oxygen metabolism was depressed by the intravenous administration of barbiturates. In our experience to date it has not been necessary to use large doses of sedation when a mixture of Apresoline and veratrum is utilized.

It is hoped that the study of cerebral circulation and metabolism may help us to understand better the disturbed physiology of the brain and come closer to rational treatment in toxemia of pregnancy.

IS TRACHEOTOMY INDICATED IN ECLAMPSIA?*†

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STANDER[1] in 1926 published a paper entitled "Studies in Anesthesia, Anoxemia, Anhydremia and Eclampsia With Certain Deductions Concerning the Treatment of Eclampsia," in which he states "the blood picture in eclampsia is so similar to that observed under anesthesia, that one wonders whether insufficient oxidation does not play a role in eclampsia. The idea seems quite plausible that any theory which tends to explain the causation of eclampsia should be linked up in some way or other with deficient oxidation." This communication is not concerned with any theory regarding the cause of eclampsia but rather with a method of increasing the patient's uptake of oxygen and the results so obtained. McCall[2] declares, "It is evident that eclampsia is a disease associated with oxygen deprivation and deficient uptake of oxygen by the brain during the convulsive stage and a compromised cellular oxygen metabolism in the presence of normal oxygen supply during the comatose phase." The results of this study seem to confirm Stander's original impression that hypoxia might play a role in the eclampsia syndrome.

Tracheotomy

Since 1949, there has been a rediscovery and popularization of the old procedure of tracheotomy. In the past few years it has been utilized in a number of conditions where hitherto management was restricted to a medical regimen or, if surgery was utilized, it was not directed toward the tracheobronchial tree. The value of tracheotomy as an adjunctive measure has been demonstrated in poliomyelitis,[3, 4] tetanus,[5] brain tumors,[6, 7, 8, 9] cerebral abscess,[10] multiple rib fractures,[11] crushing injuries of the chest,[12] and a variety of medical and surgical conditions.[13, 14] Von Leden[15] has recently published an excellent article, with an extended bibliography, describing the advantages of tracheotomy in different conditions where obstruction of the tracheobronchial tree is a problem. In two previous reports[16, 17] we emphasized the excellent results obtained in a few cases in which tracheotomy had been utilized by us as an adjunctive method in the treatment of eclampsia. To date we have used tracheotomy in 16 cases of convulsive toxemia. In addition, 4 cases of nonconvulsive toxemia exhibiting proteinuria, hypertension, coma, oliguria, and respiratory difficulty were so managed. These cases form the basis of this report.

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Altered Physiology in Obstruction of the Tracheobronchial Tree

Carter and Giuseffi[12] believe that "in the normal subject with a tidal air of 500 cc or more, the presence of a dead space of roughly 150 cc is tolerated without difficulty. This dead space in no way contributes to ultimate oxygenation, and represents unnecessary work. Therefore, in patients able to ventilate only with abnormally reduced tidal air, this constant dead space becomes more and more detrimental to the efficiency of the impaired ventilatory act." The dead space involved in the respiratory act consists of the nasal passages, mouth, pharynx, trachea, and tracheobronchial tree. They believe from experiments performed on autopsy specimens that when air enters the trachea just above the suprasternal notch as contrasted to its entrance through the nose and mouth the dead space is reduced approximately 100 c.c., and that "the more effective utilization of a tidal air which is reduced to levels incompatible with adequate ventilation by diminishing the volume of dead space appeals to the authors as an important physiological effect of tracheotomy."

It is estimated that three-fourths of the resistance to breathing is located in the upper air passage. There is increased resistance to breathing in patients with obstruction of the tracheobronchial tree, this being especially true where there are secretory obstruction and failure of the cough mechanism. The cough mechanism normally clears the respiratory tract of accumulated secretions. When there is depression or abolition of the cough reflex by coma, general debility, depression of the respiratory center, anesthesia, analgesia, or any other cause, pooling of secretions in the nasopharynx may produce almost complete obstruction and the patient may drown in her own secretions. Laryngospasm may complicate the picture. With tracheotomy there is a marked reduction in resistance to breathing, the obstructing pool of secretion is by-passed, and laryngospasm is no problem.

As a result of hypoxia or anoxia there are increased capillary permeability, pulmonary and cerebral edema, and damage of cardiac and nerve tissue. Only three to eight minutes of anoxia may result in damage or necrosis of brain cells. In cases of cardiac arrest at the time of surgery or delivery, a clear airway and administration of oxygen are the first steps in therapy—even before attempts are made to stimulate the heart. In patients whose heart action has been restored, but the interval of anoxia prolonged, convulsions may be manifest in the recovery phase.

Von Leden,[15] in discussing obstruction of the tracheobronchial tree, states: "Carbon dioxide, because of its greater molecular weight, diffuses even less than oxygen and is thus retained in the blood. This hypercapnia has not received due attention in the past; yet my own experience and that of my associates fully supports the theory that the effects of hypercapnia are even more disastrous than those of anoxia. Hypercapnia produces headache, restlessness, apprehension, disorientation and uncooperativeness in its early stages, while high concentrations induce narcosis, anesthesia, respiratory depression and circulatory collapse." He, Plum and Wolff,[18] and Blalock[19] believe that,

though oxygen saturation might be satisfactory in the presence of respiratory obstruction, hypercapnia may reach dangerous proportions.

As a result of the hypoxia and hypercapnia found in respiratory obstruction, there develops a respiratory acidosis. Due to interference with normal gaseous exchange carbon dioxide is retained in the blood as free carbonic acid (respiratory acidemia) while the hypoxia or anoxia results in the formation of excess lactic acid in the tissues and an accumulation of lactic acid in the blood (metabolic acidosis). The blood pH is lowered and may hasten the onset of coma. Von Leden[15] believes the administration of oxygen in the presence of hypoventilation is of no appreciable value in reversing the hypercapnia and acidemia, and that "the only treatment providing any real hope of success consists in removal of the obstructing secretion from the respiratory passages and reestablishment of normal alveolar ventilation."

In coma, in addition to accumulated tracheobronchial secretion, there is the problem of nasopharyngeal and salivary secretions. Also the problem of feeding and vomitus is to be considered. It is estimated that daily salivary secretion alone is in the range of 1,000 to 1,500 c.c.

Thus it is evident that in obstruction of the tracheobronchial tree there are reduced tidal air, increased resistance to breathing, hypoxia or anoxia, increased capillary permeability, pulmonary and perhaps cerebral edema, potential damage to nerve and cardiac cells, hypercapnia, and a respiratory as well as metabolic acidemia. Many vicious circles are established, viz.:

1. Anoxemia increases capillary permeability, producing pulmonary edema, which in turn increases the anoxemia.

2. Asphyxia produces a depression of the respiratory center, resulting in decreased respiratory efforts, which in turn accentuate the asphyxia.

3. Respiratory obstruction causes increased venous intrathoracic pressure, resulting in increased intracranial venous pressure, producing edema and depression of the central nervous system, which further augment the obstruction.

4. Tracheal obstruction increases venous congestion, which increases cardiac load, which may eventuate in cardiac decompensation and further venous congestion.

Rationale of the Use of Tracheotomy in Eclampsia

Since Jan. 1, 1946, there has been little change in the management of convulsive toxemia on our service other than the recent introduction of tracheotomy by one of us (C. G. C.). Tracheotomy was first performed on our service Nov. 25, 1950, and since that time has been used with excellent results in cases where we deemed it necessary. In brief, our management of convulsive toxemia, since Jan. 1, 1946, consists of sedation with morphine sulfate, Sodium Amytal, Demerol, or phenobarbital alone or in combination. Magnesium sulfate is used in many instances. The quantity of fluids administered varies according to the individual patient, neither hydration nor dehydration being our goal. Rather, fluid administration is comparable to

the regimen used by us in the treatment of lower nephron nephrosis, namely, 1,000 to 1,500 c.c. of 5 per cent glucose, sufficient to compensate for the insensible loss, plus an added quantity equal to the urinary output each 24 hours.

In addition to these methods aimed at the control of convulsions, lowering of blood pressure, and maintenance of fluid balance, attempts at assurance of an adequate airway are an important feature in management.

Many factors enter into the problem of respiratory distress and oxygenation in the eclamptic patient. Marked depression of the respiratory rate can occur as a result of the amount of sedation needed to control the convulsive seizures. Edema of the lung resulting from abnormal retention of fluids found in the eclamptic patient or from heart failure is sometimes present. Laryngospasm, occurring either spontaneously or induced by the attempted passage of an airway, is not infrequently encountered. Accumulation of secretions in the tracheobronchial tree produces respiratory obstruction. Respiratory obstruction results in the altered physiology previously discussed. Occasionally on our service exhaustion of the patient resulting from violent respiratory efforts has necessitated artificial respiration for varying periods of time. Respiratory distress and oxypenia have been so marked that the patients have exhibited cyanosis.

Relief from respiratory distress may be obtained in many cases by the use of metal or rubber airways with repeated aspirations of the pharynx, larynx, and trachea. In addition, administration of oxygen by mouth or nasal catheters is beneficial.

Brown[20] believes that secretions become less tenacious if oxygen is allowed to pass through alcohol before entering the mouth or catheter. Reich and his associates[21] recommend bubbling oxygen through 2-ethylhexanol which produces results superior to either 95 per cent or 50 per cent ethyl alcohol. We have not had any experience with these methods.

Rubber or metal airways together with suction and oxygen do not always produce the desired results. Furthermore, if left in place for more than a short period a large endotracheal tube may cause damage to the pharynx or larynx and aspiration through such a tube requires expert attendance. Obviously bronchoscopic inspection and aspiration have no place in the treatment of the critically ill patient where frequent repeated aspirations are needed. Therefore it has been our policy since November, 1950, to employ tracheotomy in the eclamptic patient in whom laryngospasm or severe obstruction to the tracheobronchial tree is present and repeated aspiration will be needed to keep an airway effective. Earlier in our experience tracheotomy was performed only if an airway and repeated suction failed. However, failure of airways and suction to relieve the obstruction in five cases observed in 1951 and the dramatic results obtained by subsequent tracheotomy in these patients led us to decide that where a long-term airway and suction would be needed tracheotomy was indicated.

Cerebral hemorrhage, cerebral softening, or meningeal hemorrhage can occur in eclamptics. Sheehan[22] found such lesions in 24 out of 67 true eclamp-

tic patients who had more than one convulsion and 14 of 31 pre-eclamptics who died in coma with no convulsions or only a single convulsion. It is estimated that no more than 3 per cent of all patients with eclampsia develop cerebral hemorrhage.[23] Utilization of tracheotomy in severe head injuries with coma and respiratory difficulties has been attended with excellent results.[6]

Tracheotomy therefore might be of value in cases of severe pre-eclampsia or eclampsia where cerebral lesions exist, for any measure of value when cerebral hemorrhage results from external trauma should benefit patients with cerebral hemorrhages from other causes. Proceeding upon this premise, we decided to employ tracheotomy as adjunctive therapy in patients with eclampsia or severe pre-eclampsia who showed marked respiratory difficulty and failed to respond to more simple methods, or who gave evidence of cerebral vascular accident, or who demonstrated severe coma.

Tracheotomy allows instant and repeated aspiration of the tracheobronchial tree as well as administration of oxygen. The pool of secretions in the hypopharynx is by-passed and the not uncommon complication of aspiration pneumonia is minimized.

Observations and Results

From Jan. 1, 1946, to May 1, 1953, there have been 80 cases of convulsive toxemia admitted to the Tulane Unit, Charity Hospital, New Orleans. From July 1, 1948, to May 1, 1953, there have been 27 cases of convulsive toxemia admitted to the Huey P. Long Charity Hospital at Pineville, La.* Thus we have been responsible for the care of 107 cases of convulsive toxemia during the period surveyed. As previously stated, tracheotomy was first used on our service in November, 1950, thus we may divide this series into the pre- and post-tracheotomy eras. The collection of cases, their distribution, the number of times tracheotomy was utilized and the mortality rates in each period are recorded in Table I. The mortality rate for the entire series of 107 cases is 6.5 per cent. We believe that a number of lives were saved by adding tracheotomy, where indicated, to our usual regimen.

In addition, tracheotomy was utilized in 4 cases of nonconvulsive toxemia exhibiting coma and marked respiratory distress. There were no deaths in the latter group.

As previously demonstrated, there is a trend toward a lower mortality rate when tracheotomy is utilized in convulsive toxemia. Therefore, the remainder of this analysis will concern observations and results obtained in 20 cases (Table II) in which tracheotomy was utilized in convulsive or nonconvulsive comatose patients showing respiratory obstruction. Eclampsia was found in patients from age 16 to 36 years (Table III) and gravidity and parity ranged from gravida i, para 0, to gravida viii, para vii.

*Since July 1, 1948, the Department of Obstetrics and Gynecology, Tulane University, has been responsible for the Obstetric and Gynecologic Services at the Huey P. Long Charity Hospital, Pineville, La., as a "farming out" project. Senior residents from the Tulane Unit, Charity Hospital, are rotated through the Huey P. Long Hospital and are in complete charge of the Division of Obstetrics and Gynecology, aided by weekly consultation visits by members of the Department of Obstetrics and Gynecology, Tulane University.

TABLE I. RESULTS IN CONVULSIVE TOXEMIA

PERIOD	NO. OF CASES	TRACHEOTOMY	SURVIVED	DIED
1/1/46 to 11/1/50	62	0	57	5 (8%)
11/1/50 to 5/1/53	45	16	43	2 (4.4%)

TABLE II. TRACHEOTOMY SERIES

Convulsive	
a. Antepartal	13
b. Postpartal	3
Nonconvulsive	4
Total cases	20

TABLE III. AGE

YEARS	15-20	20-25	25-30	30-35	35-40
Convulsive	6	2	4	2	2
Nonconvulsive	2	0	0	2	0
Total	8	2	4	4	2

It is to be emphasized that though the principal indications for tracheotomy are listed in Table IV, all patients demonstrated marked respiratory difficulties and great increase in tracheobronchial secretions. In one case respirations had ceased entirely on admittance but were promptly resumed following tracheotomy and artificial respiration. Some patients exhibited cyanosis prior to tracheotomy. In all cases tracheotomy was followed by immediate improvement in respiration. Furthermore, it is the impression of our residents, fellows, and staff that, following tracheotomy, *less of the hypnotic drugs is required for adequate sedation than prior to tracheotomy or where tracheotomy was not utilized.*

TABLE IV. PRINCIPAL INDICATIONS FOR TRACHEOTOMY*

Labored respiration	8
Laryngospasm	7
Respiratory rate less than 10 per minute	1
Respiratory rate less than 5 per minute	3
No respiration on admittance	1
Total cases	20

*All cases demonstrated marked respiratory difficulties and great increase in tracheobronchial secretions. *Only the outstanding symptom in each case is listed.*

The type of delivery and time of delivery as related to tracheotomy are listed in Table V. In 3 cases convulsions were postpartal in origin. Delivery was equally divided between the vaginal route and by cesarean section. Of the 9 patients delivered by cesarean section, 3 had severe abruptio placentae as well as convulsive toxemia, 3 had nonconvulsive toxemia and were in severe coma with "unripe" cervices, while 3 had convulsive toxemia with long, rigid, undilated cervices.

Of the patients having cesarean section as well as tracheotomy, one died on the twenty-fifth postpartal day. An abstract of her history is presented later in this communication.

TABLE V. DELIVERY

TYPE	VAGINAL		CESAREAN	
TRACHEOTOMY	PRE	POST	PRE	POST
Convulsive	3	7	0	6
Nonconvulsive	0	1	0	3

Anesthesia for delivery following tracheotomy (Table VI) did not present any problem. In all cases the tracheotomy tube was removed by the tenth post-tracheotomy day. The vast majority of the tubes were removed on the fifth day. There were no complications nor any case of post-tracheotomy aphasia. In no case was hospitalization extended because of tracheotomy (Table VII). In 6 cases respiratory symptoms were so severe that tracheotomy was performed within one hour of admission to the hospital. The longest interval from admission to tracheotomy was 48 hours (Table VIII).

TABLE VI. POST-TRACHEOTOMY ANESTHESIA FOR DELIVERY

TYPE OF DELIVERY	ANESTHESIA		
	NONE	LOCAL	GAS-OXYGEN
Vaginal	2	5	1
Cesarean section		7	2
Postpartal eclampsia			3 cases

TABLE VII. TRACHEOTOMY

DAYS	2	3	5	7	10	11	12	13	14	18	20	21	25	32
Tracheotomy tube removed	1	4	11	3	1									
Hospitalized post partum	1*			3	3	2	4	0	1	2	1	1	1*	1

*Died.

TABLE VIII. TIME FROM ADMISSION TO TRACHEOTOMY

HOURS	0-1	1-6	6-12	12-24	24-48	48+
Convulsive	6	4	1	1	3	1
Nonconvulsive	0	0	1	2	1	0

There were two deaths. A brief extract of each of these cases follows:

CASE 1.—B. K., a 20-year-old Negro woman, gravida i, para 0, about 38 weeks pregnant, was admitted with coma, convulsions, laryngospasm, hypertension, albuminuria, edema, and coarse râles throughout both lung fields. No fetal heart tones were heard and definite evidence of a dead fetus and abruptio placentae was present. Sedation was given but did not improve the respiratory difficulty, so tracheotomy was performed 45 minutes after admission. Respiration immediately improved. The following day the patient's condition was generally improved but evidence of increasing severity in the signs and symptoms of premature separation of the placenta necessitated cesarean section under general anesthesia. A severe Couvelaire uterus was encountered which would not contract following removal of the baby, therefore cesarean hysterectomy was performed. One unit of fibrinogen was administered immediately for constant ooze from the wound edges. Following administration of fibrinogen, oozing of blood stopped. The tracheotomy tube was removed on the tenth postpartal day. On the twelfth postoperative day because of a serosanguineous drainage from the wound the patient was taken to the operating room and

the wound examined under general anesthesia. It was found that the fascia had separated but the peritoneum was intact. Secondary closure of the wound was performed. From then on recovery was steady. The patient was ambulatory on the twenty-first postoperative day. A mild generalized convulsion followed by Jacksonian-type convulsions developed. During the entire postpartal course the blood pressure varied between 142/80 and 184/118. On the twenty-fifth postoperative day she had a generalized convulsion. Reconsultation with the Departments of Medicine and Neurosurgery led to the diagnosis of hypertensive encephalopathy. Lumbar puncture showed clear fluid at a pressure of 330 mm. of water. There was no respiratory difficulty from the time the tracheotomy tube was removed until the series of convulsions on the twenty-fifth postpartal day at which time the patient died. Permission for autopsy was not granted.

CASE 2.—L. S., 21-year-old para 0, gravida i, was admitted to the Huey P. Long Charity Hospital at Pineville, La., on June 14, 1951. She was approximately 28 weeks pregnant and had hypertension, edema, proteinuria, coma, and convulsions. Râles were found in both lung fields. Sedation, nasal oxygen, intravenous fluids, and digitalis were administered. Twenty-four hours later, the patient was in poor condition, the blood pressure was 118/60, she remained in coma, and marked respiratory difficulties developed. A tracheotomy was performed with improvement in respiration but the patient died a few hours later. Autopsy showed marked edema of the brain but no softening or hemorrhage.

Tracheotomy was of benefit in the acute phase of the illness of Case 1, the patient dying 13 days following removal of the tracheotomy tube and apparent recovery. In the light of more experience, we believe that tracheotomy should have been performed earlier in the latter case, admitting that it is a matter of conjecture whether or not the ultimate results would have been different.

Summary and Conclusions

The problems encountered in successful management of eclampsia are many and varied. Convulsions, coma, urinary suppression, hypertension, altered electrolyte and fluid balance, proteinuria, edema, and respiratory difficulties are manifest. In addition problems related to time and type of delivery arise. Moreover, severe abruptio placentae is sometimes encountered. Whether or not these are terminal symptoms of an abnormal vasopressor activity,[24] there has not as yet been any specific single therapeutic agent that produces excellent results in all cases in all hands. Therapy in eclampsia is as varied as the theories of its origin. Also, we frequently have patients admitted to our service who have had little or no prenatal care and exhibit obstetric complications of an advanced degree. Respiratory distress is a symptom often encountered in our eclamptic patients. Of the 5 patients who died in the pretracheotomy era, 4 did so within 24 hours of admission. The other died 4 days after entry but all 5 *exhibited marked respiratory distress.*

No matter what basic therapy is utilized in eclampsia, be it sedation or antispasmodics, eclamptic patients still die. Many of those who die have cerebral hemorrhage. We cannot speak for services in other hospitals, but we can emphasize that of the eclamptic patients who died on our service the vast majority had respiratory distress of a severe degree. Tracheotomy is of value in cerebral hemorrhage from trauma and also in many other medical and surgical conditions where respiratory obstruction is encountered. We

believe that we have saved a number of lives by its use as an adjunctive measure in the management of eclampsia with respiratory distress, or of severe pre-eclampsia with coma and respiratory embarrassment. Waldrup[25] of the Independent service at Charity Hospital, New Orleans, states, "Since January 1, 1951, tracheotomy has been used in treating four (4) convulsive toxemia patients on the Independent service. Of these four cases, tracheotomy was used in three to facilitate tracheo-bronchial aspiration, by-passing laryngeal obstruction, relieving marked hypoxia. The fourth was a proven case of subarachnoid hemorrhage. There was prompt relief of respiratory difficulty with improvement of oxygenation. All four cases survived. We are of the opinion that tracheotomy is definitely indicated in the treatment of convulsive toxemias experiencing respiratory difficulty and hypoxia and in cases where intracranial hemorrhage is proven or suspected."

Tatum[26] of the Louisiana State University service at the same institution declares, "During the past two years there have been five eclamptics on our service. We performed tracheotomies on two of these patients, and it is my feeling that these two were definitely benefited by the procedure. Our criterion for tracheotomies is to provide a satisfactory airway by the least traumatic method. In these two cases, repeated aspirations were necessary, and it was felt that the repeated trauma of aspirations would be more deleterious to the patient than would a tracheotomy. In other words, the feeling of the department is that tracheotomies are less traumatic than the frequently repeated aspirations for the purpose of maintaining a clear airway."

From our experience and that of our colleagues at Charity Hospital, New Orleans, we believe that tracheotomy has a definite place as an adjunctive measure in the therapy of eclampsia.

A ready tracheotomy set should be a part of the equipment on all obstetric units. Professional personnel should be conversant with the technique of tracheotomy as an otolaryngologist is not always available when an emergency tracheotomy is necessary.

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Discussion

DR. CURTIS J. LUND, Rochester, N. Y.—So long as the treatment of eclampsia is symptomatic, so long should every potentially valuable therapeutic lead be explored. Dr. Collins and his associates have commendably revived the old, if not venerable, operation of tracheotomy with a distinctly modern touch.

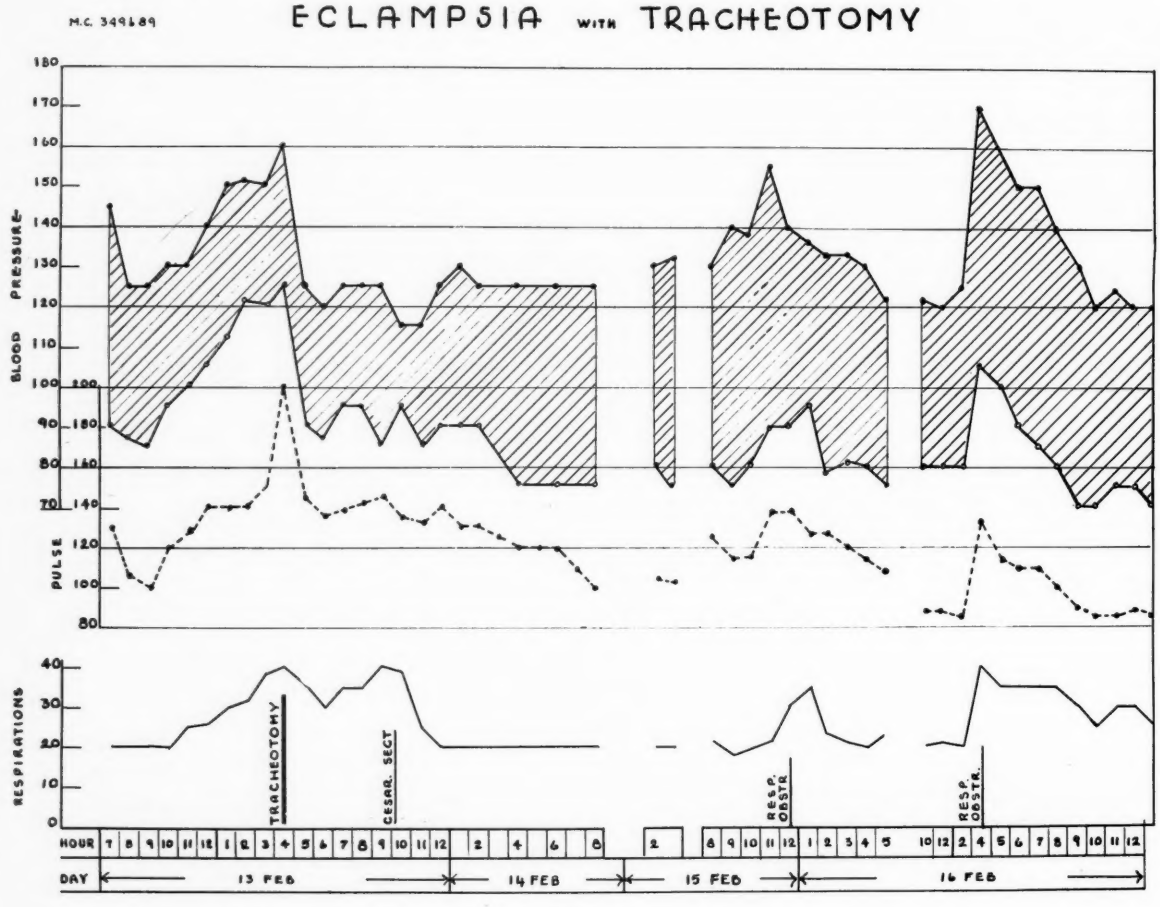

Fig. 1.

There must be few obstetricians who fail to recognize the need for oxygen therapy in the anoxia of eclampsia. Too often it is token therapy, while the patient's oxygen want deepens because of unrecognized respiratory obstruction. However, it is paradoxical that few obstetricians recognize the poisonous effects of increasing concentrations of carbon dioxide. Dr. Collins has wisely emphasized the significance of hypercapnia and respiratory acidosis which may exist independently or concurrently with hypoxia. The effect of hypercapnia upon the heart is great, possibly greater than that of anoxia.

Our experience with tracheotomy has been small but assuredly satisfactory. Fig. 1 shows the effects of tracheotomy upon blood pressure, pulse, and respirations in a patient with eclampsia. This patient responded to the customary therapy and her convulsions had ceased prior to the beginning of this graph. After a stable period without evidence of respiratory obstruction, cardiac failure followed by pulmonary edema appeared. The vicious cycle was now established and was not reversed until tracheotomy was done. Upon several occasions after delivery, respiratory obstruction with hypercapnia occurred. Each time the rapidly rising pulse, blood pressure, and respiratory rate were relieved by prompt aspiration through the tracheotomy tube. Indeed, the most severe obstruction produced massive atelectasis and would probably have been fatal had not the aspiration been done quickly and readily through the tracheotomy tube.

The drama of eclampsia is powerful upon students and staff, but when tracheotomy is added the impact is intense. To avoid the production of overenthusiasm in those without experience, some of the disadvantages should be cited. Tracheotomy increases rather than decreases the need for medical and nursing care. Competent nurses must be constantly present to see that the special equipment for humidification and aspiration is in order and, above all else, to see that the patient does not suffocate from sudden obstruction of the tube. There is little doubt that the trauma of the tracheotomy tube and the suction tube produce irritation, cough, and increased secretions. Then, too, some critics of tracheotomy deny its use for cosmetic reasons. Such specious arguments are of little moment when the patient may be facing death from respiratory failure.

Is tracheotomy indicated in eclampsia? Indeed it is. However, the indication, as Dr. Collins has clearly said, is the respiratory distress of eclampsia. When each patient is intelligently and individually treated, some will need and will be benefited by the adjunctive therapy of tracheotomy.

DR. COLLINS (Closing).—I want to thank Dr. Lund for his discussion and for his projecting the beautiful slide showing the effect of tracheotomy on respirations, blood pressure, and the heart. We do not have any laboratory proof that we are oxygenating the blood any better; our evidence is all symptomatic, In one case we did attach an oximeter to the ear and obtained an oxygen saturation which was 86 per cent in the lobe of the ear before tracheotomy and four minutes after tracheotomy it was 94 per cent. We cannot generalize on one case, but I am sure you are aware of the problems involved in doing basic research on the woman in convulsions.

THE MECHANISMS OF BLEEDING DURING PREGNANCY*

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IN MOST forms of life, perpetuation of the species is accomplished without attending risk of hemorrhage to the mother. Veterinarians state that hemorrhage is apparently nonexistent among domestic animals. Nissen and Yerkes[1] state that the reproductive process in the chimpanzee is occasionally accompanied by slight bleeding in the early stages and in a personal communication mention the occurrence of a copious hemorrhage late in pregnancy, followed by stillbirth. It is known that variations exist in the structure and circulation of the placenta among vertebrates, but it is only in the human being and possibly the primates that the development of a blood shunt in the maternal uteroplacental circulation sets up potentialities of serious hemorrhage.

Elsewhere in the body, the embryological development of permanent vascular channels provides elastic and muscular elements in the structure of the vessel wall which are able to withstand the stress of blood pressure and trauma. By contrast, the development of a blood shunt, interposed in the uterine circulation, imposes a liability to hemorrhage due to the fragile character of the membrane-walled blood channel at the periphery of the placenta—the marginal sinus—which serves as an intermediary communication between the outgoing intervillous maternal blood and the uterine veins beneath the periphery of the placenta, through which the maternal blood is returned to the general circulation.[2]

It has been proved by Spanner[3] and verified by Ramsey[4] and Earn and Nicholson[5] that, when a maternal blood supply to the placenta is established by chorionic erosion, the intervillous maternal blood does not leave by way of eroded maternal veins near the point of entrance, but ascends through intervillous spaces to the chorionic plate, thence in all directions to the marginal sinus at the periphery of the placenta where communications are formed with the uterine veins. Venous injection of colored material into rare specimens in which the predelivery utero placental connection and circulation are undisturbed shows venous filling into the marginal sinus but not into the blood lakes beneath the placenta; arterial filling progresses from the blood lakes beneath the placenta through the intervillous spaces, thence outward beneath the chorionic plate to the marginal sinus and into the uterine veins.

The marginal sinus is therefore formed during the first trimester. It varies from 0.5 to 1.2 cm. in diameter,[3] the roof and outer wall consisting of a fusion of

*Presented at the Seventy-sixth Annual Meeting of the American Gynecological Society, Lake Placid, N. Y., June 15 to 17, 1953.

the decidua reflexa, chorion laeve, and amnion, which is continuous with the decidua vera and the membranes beyond the placenta; the floor is decidua vera in which openings appear communicating with uterine veins; the inner wall is fibrinous in places and is often in direct communication with the intervillous spaces. The lumen may seem to disappear at intervals and is not a continuous channel. The stage at which full development and reinforcement of the marginal sinus by the membranous layers and the pressure of the amniotic fluid are attained coincides with the stage at which the frequency of unexplained bleeding diminishes toward the end of the third month of pregnancy.

Since the mechanism of bleeding bears some relation to a certain stage of pregnancy, it will be appropriate to consider bleeding chronologically according to each trimester of pregnancy, based on the date of the last period and not on the supposed date of conception. Fortunately, with increasing knowledge of the placenta circulation, both fetal and maternal, there is less need of designating certain hemorrhages of pregnancy as idiopathic.

Variations in the color of bleeding at any time during pregnancy are directly related to the amount of bleeding and the length of time required for the blood to appear externally. A slight amount of bleeding, bright red at its source, becomes dark or even brown, if the blood escapes slowly. A larger amount of blood escaping rapidly does not have time to change to a dark or brown color until after some hours or days when the residue in the uterus gradually escapes. Hence, if the source of bleeding is low near the cervix, bleeding is more likely to be bright; if high, dark or brown.

As a basis for analysis the records of 3,125 consecutive private patients observed throughout pregnancy, were reviewed, to obtain cases of bleeding in any visible amount one or more times during pregnancy.

TABLE I. ANALYSIS OF 3,125 CONSECUTIVE OBSTETRIC CASES IN PRIVATE PRACTICE AS TO BLEEDING OF ANY VISIBLE AMOUNT DURING PREGNANCY

Bleeding occurred in	1,037 cases or 33.2%
Solely in first trimester in	694 cases or 66.9%
Solely in second trimester in	99 cases or 9.5%
Solely in third trimester in	90 cases or 8.7%
More than one trimester in	154 cases or 14.8%

The over-all frequency of bleeding during pregnancy was found to be 33.2 per cent. It is evident that bleeding occurred much more frequently in the first trimester. The increased susceptibility to bleeding in this period is apparently due to (1) erosive effects of the chorionic tissue on the decidual arterioles at the time of implantation, (2) inadequate hormonal support to the decidua, in cases in which there is embryological failure or interruption of development of the embryo or fetus, and (3) establishment of a blood shunt in the uterine circulation during formation of the placenta.

Implantation bleeding, if present, necessarily occurs at or very near the time of the first missed period. It is the result of the earliest erosive action of the chorionic tissue on small decidual vessels. Being small in amount, it becomes brown during its slow escape from the birth tract. If it does not continue or recur, the prognosis is good.

In 1,037 consecutive cases in which bleeding occurred during pregnancy, slight brown discharge appearing at or within a few days of the time of the first missed period and not requiring protection occurred in 200 cases, or 19.3 per cent. Abortion followed implantation bleeding, solely, in 7 cases, or 3.5 per cent. It is probable that implantation bleeding, alone, has no etiological significance, if abortion occurs some time later.

TABLE II. RELATION OF INITIAL COLOR OF POSTIMPLANTATION FIRST TRIMESTER BLEEDING IN 628 CASES TO NUMBER OF ABORTIONS (147), TYPE OF PRODUCT, AND CAUSE OF BLEEDING

PRODUCT SEEN (147)	CASES	BROWN	RED
1. Decidual cast or empty sac	104	64 (61.6%)	40 (38.4%)
2. Amorphous embryo or deformed	12	8 (66.6%)	4 (33.4%)
3. Macerated	26	11 (42.6%)	15 (57.4%)
4. Apparently healthy	5	3 (60.0%)	2 (40.0%)

Cause of bleeding probably hormonal in Nos. 1, 2, and 3.

Bleeding in the first trimester, other than that appearing at the time of the first missed period, occurred in 628 cases, or 20.0 per cent. Abortion followed in 147 cases, or 23.4 per cent, in all of which the products were available. There was no recognizable conceptus in 104 cases, or 70.8 per cent; a macerated embryo or fetus was found in 26 cases, or 17.6 per cent; a deformed fetus or amorphous embryo in 12 cases, or 8.3 per cent; an apparently healthy embryo or fetus was found in 5 cases, or 3.3 per cent. Initial brown discharge predominated irrespective of the presence or absence of a recognizable conceptus.

If the embryo or fetus fails to develop or is maldeveloped, hemorrhage and abortion usually occur after a variable lapse of time. The mechanism by which bleeding occurs is apparently hormonal, similar to that of menstruation, but much heavier due to the additional source at the placental site. A defective product of conception is apparently associated with a defective placenta. The resulting deficiency in hormone (progesterone?) apparently induces hemorrhage from breakdown of the decidua, following spasm of the spiral arterioles. Bleeding begins very gradually, appearing as a brown discharge, which, after a variable number of days—usually three to five days—becomes red. Abortion becomes imminent, when the flow requires frequent change of pads, forms clots, and is accompanied by regular pains. Insufficient height of the fundus for the stage of pregnancy usually portends such an outcome. Facilities for assay of pregnandiol were not available in this study.

Bleeding may occur in a sequence, the reverse of brown to red. It appears suddenly, bright red, and may be of rather large amount, but diminishes within a few hours or days to a brown show. This type of bleeding, while apparently more threatening at the time, is usually compatible with continuation of pregnancy and shows an enlargement of the uterus consistent with the stage of pregnancy.

The bleeding in this case occurs by an entirely different mechanism and is concerned with the formation of the marginal sinus. When erosive action of chorionic tissue on decidual arterioles permits a free pressurized flow of blood

upward through the intervillous spaces to the chorionic plate (Fig. 1), thence outward in all directions beneath the chorionic plate to the periphery of the placenta, the flow meets resistance at the junction of the decidua reflexa and vera. Apparently, at this point, the decidua may be unable to contain the pressure of the maternal blood stream and a breakthrough occurs, the blood from which may be concealed or expelled. If concealed, the resulting irritation may account for vague cramplike pains early in pregnancy, the cause for which has always been difficult to determine. At term delivery, a thin layer of gray puttylike fibrin adherent to the membranes or a placenta marginata gives proof of the previous hemorrhage. Occasionally, the irritation from the concealed clot is sufficient to cause abortion some weeks or months later.

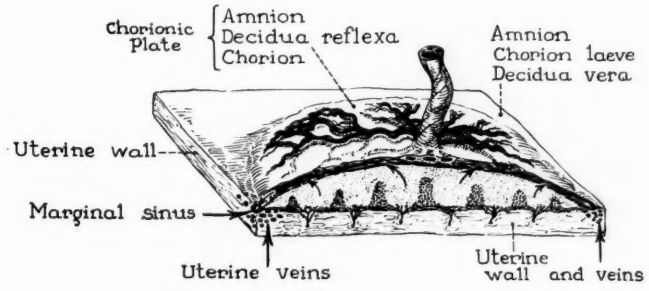


Fig. 1.—Diagrammatic representation of the course of the maternal blood from the decidual arterioles upward through the intervillous spaces to the chorionic plate, thence outward in all directions to the marginal sinus at the periphery of the placenta, where communications with uterine veins return the blood to the general circulation.

If the extravasation does not undermine the membranes, it may cause an inward folding of these layers over the border of the placenta, forming a circumvallate placenta (Fig. 2). Marked encroachment of this fibrin fold on the surface of the placenta may interfere with the maternal circulation in the marginal sinus and the fetal circulation on the surface of the placenta and cause occasional hemorrhage or underdevelopment of the fetus. A lesser degree of breakthrough along the marginal sinus gives rise to placenta marginata, the fibrin deposit encircling but not folding over the margin of the placenta.

Of 49 cases in which a circumvallate placenta was found, some of which were in this series, 19, or 28 per cent, had had external bleeding during pregnancy. In the remainder, bleeding had occurred as evidenced by a circumvallate appearance, but remained concealed. The significance of these patterns as to the amount and color of the initial bleeding at this stage of pregnancy was emphasized by Colvin and associates[6] in 1950.

The mechanism of external bleeding in ectopic pregnancy is that of a reflux flow from the site of chorionic erosion of the tube wall, appearing

usually as an intermittent slight red or brown show. It may also be hormonal, due to death of the embryo and casting off of the decidua. It is remarkable that no case of ectopic pregnancy was found in this series.

The mechanism of bleeding in hydatidiform mole is apparently that of a loosening of the fastening villi as they become cystic or an exaggerated erosive effect of the chorionic tissue. Severe bleeding may well occur, as stated by Hertig, quoted by Reid,[7] by disruption of the marginal sinus from peripheral expansion of cystic villi beyond the boundaries of the placenta, thus removing a vital link in the path by which the maternal blood is returned to the general circulation.

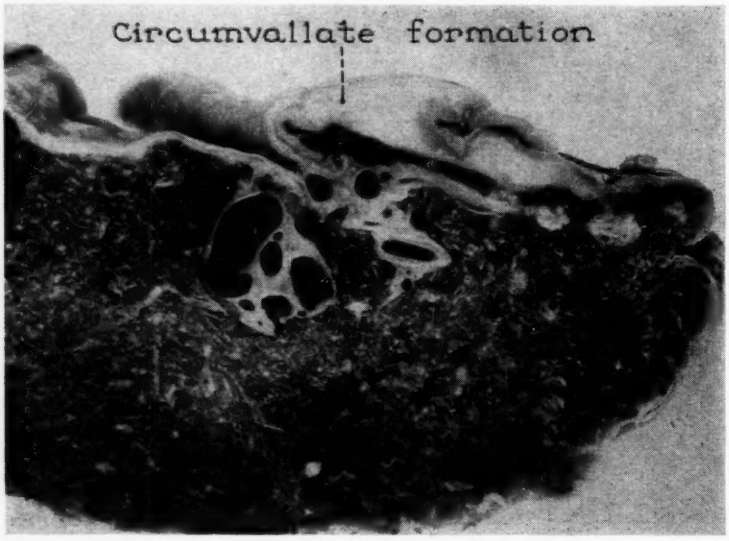


Fig. 2.—Placenta circumvallata resulting from marginal sinus rupture and hemorrhage early in pregnancy, which raised and folded the membranes over the margin of the placenta. A thick layer of yellow-white fibrin remains which, in some cases, may interfere with circulation in the fetal vessels or functioning of the marginal sinus. Hemorrhage of a lesser degree creates the appearance termed placenta marginata, in which the residue of fibrin merely encircles the placenta but does not fold over its border.

Slight bleeding was associated with genital pathology in 32 cases of the entire series including such conditions as cervicitis, cervical polyp or erosion, double uterus, fibroid uterus, and vaginitis. Bleeding due to submucous fibroid, carcinoma of the cervix, or varicosities involving the genital tract did not occur in this series. If not discovered at the first prenatal visit, later investigation will identify these causes of slight bleeding.

Trauma apparently accounted for slight bleeding in 43 cases of the entire series, or 4.1 per cent, and was most frequently due to coitus, occasionally to falls or accidents.

Bleeding occurs much less frequently in the second trimester. This is probably explained by the fact that defective products have usually been expelled before the fourth month. However, the irritating effects of old hemorrhage around the margin of the placenta from marginal sinus rupture in the first trimester may not cause abortion until the second trimester. Also some missed abortions carry over into the second trimester.

As will be seen from Table III, although fewer patients bled in the second than in the first trimester, a greater proportion of them aborted. However, if there is evidence of good development at the end of the first trimester, the prognosis for continuation of the pregnancy is good. As will be seen later, the incidence of premature labor is increased.

TABLE III. RELATION OF INITIAL COLOR OF POSTIMPLANTATION SECOND TRIMESTER BLEEDING IN 192 CASES TO NUMBER OF ABORTIONS (67), TYPE OF PRODUCT, AND CAUSE OF BLEEDING

PRODUCT SEEN (67)	CASES	BROWN	RED
1. Decidual cast or empty sac	10	6 (60%)	4 (40%)
2. Amorphous embryo or deformed	3	0 (0%)	3 (100%)
3. Macerated	27	3 (11.1%)	24 (88.9%)
4. Apparently healthy	27	1 (7.4%)	25 (92.6%)

If conceptus present, initial bleeding predominantly red (88 to 100%). Cause: marginal sinus (11); abruptio (1); placenta previa (2); hormonal (10); unknown (43).

As might be expected, bleeding is greater in amount in this period, and hence predominantly red at the onset. It is more often possible to attribute the bleeding to a well-defined cause, such as rupture of the marginal sinus, placenta previa, and occasionally abruptio placentae. The role of hormonal deficiency as a cause is more difficult to assess, hence bleeding of unknown origin must be admitted in more than half of the cases.

Comparing the products of abortion, it is noted that absence of the conceptus occurred much less frequently. A recognizable or healthy product was much more frequently seen.

The third trimester introduces possibilities of occurrence of the more serious types of hemorrhage, based upon other mechanisms of bleeding. The marginal sinus, however, still plays an important role. Close inspection of placentas following labors complicated by amounts of bleeding sufficient to be of concern to the attendant has definitely indicated that the lower the site of implantation of the placenta, the greater the frequency of rupture of the marginal sinus.

The reason for this apparently lies in the greater stretch and strain put upon the membranes and sinus, due to increasing Braxton Hicks contractions in the latter part of pregnancy. Fig. 3 illustrates the manner in which rupture of the marginal sinus may occur when the margin of the placenta is near, on, or partially over the rim of the cervical opening.

It has always been thought that the mechanism of hemorrhage in cases of low implantation of the placenta was through an inequality of pull of Braxton Hicks contractions or labor pains on the lower uterine segment and the previal portions of the placenta. Examination of the placentas from such cases, however, fails to show accumulated adherent blood separating the uteroplacental attachment, but has shown rupture and thrombosis of the marginal sinus, the marginal sinus thrombus often showing continuity with the extravasated blood adherent to the membranes along the margin of the placenta.

If the placenta is implanted totally over the cervix, a different mechanism of bleeding is apparently involved. In this case, it is the placenta, not the

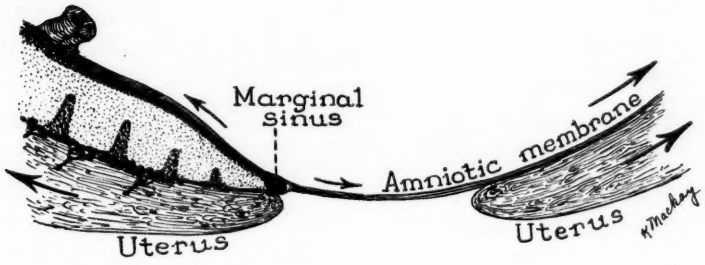
membranes and marginal sinus, which is under stretch and strain during Braxton Hicks contractions (Fig. 4). The previal portion of the placenta constitutes an area in which there is an intervillous vacuum of blood pressure, since there are no underlying decidual arterioles forcing maternal blood upward between the villi. The decidual septa, extending two-thirds of the distance toward the chorionic plate, apparently prevent lateral flow into the pressureless previal area. However, the pressurized maternal blood flowing beneath the chorionic plate toward the periphery is free and physically disposed to descend into the pressureless previal area. Since the villi in this area are poorly supplied with blood, there is sufficient chorionic tissue degeneration, demonstrable microscopically, to liberate thromboplastin, induce intervillous thrombosis, and temporarily check bleeding.

Increasing stretch of the placenta, due to increasing Braxton Hicks contractions nearer term, may reopen the thrombosed intervillous spaces, causing repeated hemorrhages. This mechanism of bleeding is diagrammatically illustrated in Fig. 5. The patient from whom this placenta was reproduced experienced a succession of five hemorrhages from 6½ to 8½ months, replacement transfusion being given on each occasion, when warranted by the amount of blood loss. At the time of the final hemorrhage, cesarean section was performed and the entire thickness of the previal portion of the placenta previa was found to be studded with numerous intervillous thrombi, the black appearance and firm consistency of which indicated an age corresponding to previous hemorrhages. Unfortunately, this placenta was not photographed, but the artist's reproduction of the appearance is substantially correct.

The placenta shown in Fig. 6 was obtained from a case of total placenta previa in which brown discharge occurred during the thirty-seventh week, followed by a moderately severe hemorrhage in the thirty-eighth and again in the fortieth week. Expectant treatment and blood replacements were carried out. A vaginal examination following the final hemorrhage revealed total placenta previa. Cesarean section was performed and the mother and baby survived.

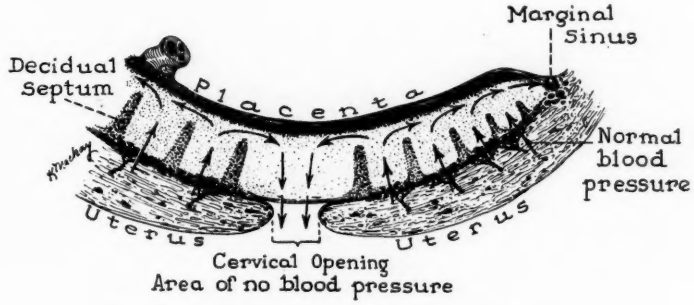
It will be noted that there is poor development of the villi in the previal area, the maternal side of this area being lined with dark recent clot and lighter old fibrin of previous hemorrhages. Directly above this craterlike area there is seen a wedge-shaped black area of thrombosed maternal blood which has descended from the chorionic plate. It presents a broad base toward the plate indicating the point of origin, and a narrowing toward the point of exit over the cervical opening. This thrombosed blood was derived from the subchorionic blood stream, which descended into the pressureless previal area.

It is therefore probable that hemorrhage in total and to some extent in partial placenta previa is due to the existing differential in blood pressure between the previal and the adjacent nonprevial portions of the placenta. In marginal, low-lying, and to some extent in partial placenta previa, hemorrhage is due to rupture of the marginal sinus. Stated in another way, in total



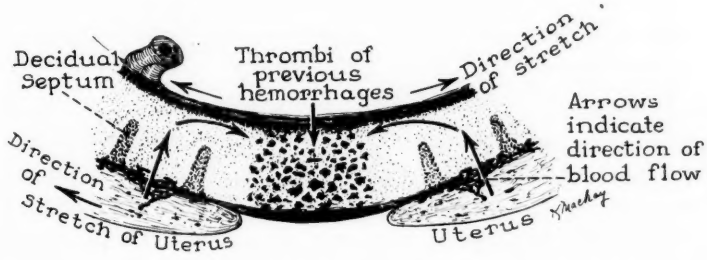
Marginal Sinus Involvement in
Either Partial or Low-lying Placenta Previa

Fig. 3.—Diagrammatic representation of marginal placenta previa. Rupture of the marginal sinus, resulting from tension on the membranes during Braxton Hicks contractions or labor pains, is the probable cause of bleeding in low-lying, marginal, and partial placenta previa, rather than a disruption of the attachment of the placenta and decidua just within the cervical rim. Evidence of rupture of the marginal sinus is easily demonstrated in many specimens.



Blood Pressure Differentials in
Total Placenta Previa

Fig. 4.—Diagrammatic representation of total placenta previa, showing the effect of the vacuum of blood pressure in the ischemic previal portion of the placenta, as it influences the pressurized maternal blood stream beneath the chorionic plate to turn from its peripherally directed course and descend into the previal area, thus causing hemorrhage.



Probable Mechanism of Hemorrhage in
Total Placenta Previa

Fig. 5.—Diagrammatic representation of the gross appearance of the previal area in a case of total placenta previa, carried nearly to term by expectant treatment and blood replacements for a succession of hemorrhages. The previal area was studded with old thrombi representing previous hemorrhages. The evidence favored descent of blood from the subchorionic-plate blood stream rather than uterodecidual disruption within the rim of the cervix as the cause of the hemorrhages.

placenta previa stretch is applied to the placenta itself; in partial, marginal, and low-lying placenta previa, stretch is applied to the marginal sinus through the attachment of the membranes.

Finally, there remains another severe form of hemorrhage, occurring mainly in the third trimester, namely, from abruptio placentae, the mechanism of which has long been obscure, but in the light of more recent investigations is becoming better understood.

There is much evidence to indicate that biochemical factors initiate hemorrhage in abruptio placentae. An understanding of the uteroplacental and fetal placental circulations is essential to an understanding of the manner in which biochemical changes occur in the placenta and produce abruptio hemorrhage.

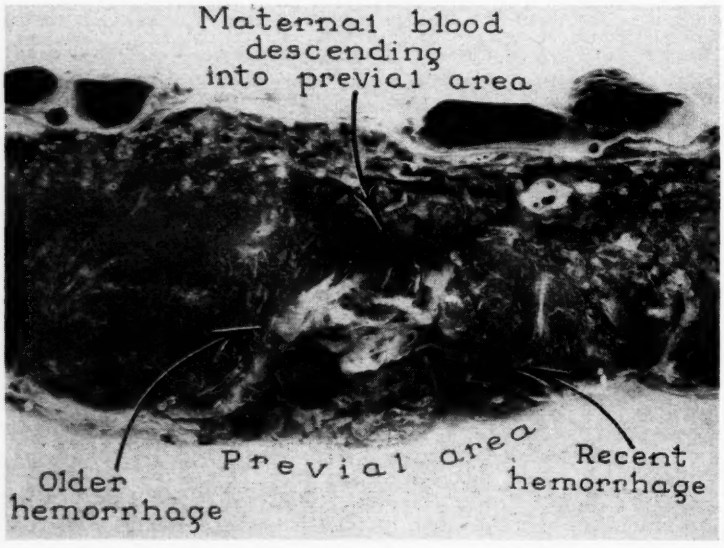


Fig. 6.—Placental strip from a case of total placenta previa, showing hypoplasia of the villi in the craterlike previal area and evidence that former hemorrhage descended from the subchorionic-plate blood stream into the previal area. White fibrin and dark adherent clots lining the previal surface indicate the age difference of corresponding previous hemorrhages.

The vitality of the chorionic epithelium covering the villi is dependent on a free and open maternal intervillous circulation. Narrowing or obliteration of the intervillous circulation may be produced by any process which causes excessive enlargement of the villi. The hydropic degeneration of the stroma of the villi in hydatidiform mole and the edematous condition of the villi in erythroblastotic placentas produce this effect by enlargement and crowding of the villi. In each of these conditions, deficiency of intervillous maternal circulation may cause necrosis of the chorionic epithelium and be followed by toxemia.

There exist in the placental veins definite smooth-muscle sphincters, first described by Spanner[3] (Fig. 7), and verified by us[8] (Figs. 8, 9, 10, 11, and 12) and by Earn and Nicholson.[5] They no doubt have a definite physiological function, possibly that of preventing an overloading of the fetal heart from pressure effect on the placental veins. However, if overstimulated by hormonal

action, probably oxytocin, as suggested by results of recent experiments,[8] exit of fetal blood through the placental veins must be obstructed, causing dilatation of the villous capillaries, enlargement and crowding of the villi, narrowing or obliteration of the intervillous spaces, restriction or exclusion of the maternal blood, with resulting anoxic necrosis of the chorionic epithelium.

This is the specific gross and microscopic appearance found in placentas from cases of pre-eclampsia, eclampsia, and abruptio placentae. It is readily demonstrable, provided the placenta has been fixed for three or four weeks in 10 per cent formalin and cut in strips not more than 1 cm. in width. The gross infarction was first noticed in cases of toxemia by Young[9] and verified by us,[10] Patterson, Hunt, and Nicodemus,[11] Falkiner,[12] Steigrad,[13] and Zeek and Assali.[14] We have demonstrated that the placental pathology in abruptio placentae is identical with that found in pre-eclampsia and eclampsia.

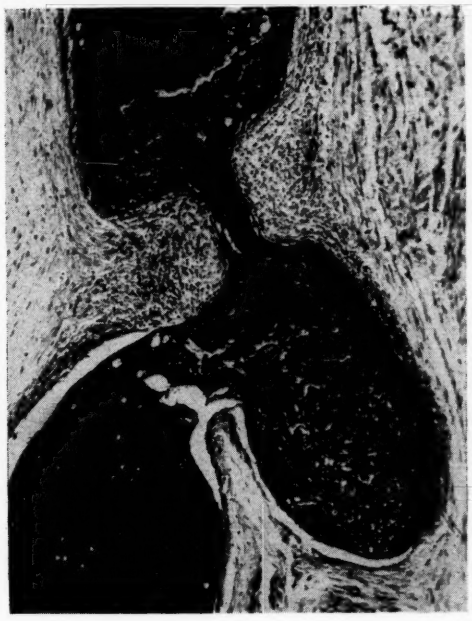


Fig. 7.—Spanner's[3] illustration of a placental vein sphincter.

Depending on the number and location of the veins so obstructed by sphincter action, the dependent units of placental tissue appear grossly as sharply circumscribed, slightly firm, black, round or oval areas in the acute stage but slightly brown in the subacute stage, in marked contrast to the surrounding lighter normal placental tissue. The lesion may be localized or may be very extensive involving most, if not all, of many strips. Microscopically, the villous capillaries, which normally are not wider than two or three red cells abreast, are dilated to a width of ten to twenty or more red cells, or occasionally ruptured; the intervillous spaces are nearly, if not entirely, obliterated and the nuclei of the chorionic epithelium show pyknosis, karyorrhexis, or karyolysis according to the stage of necrosis. More detailed description of these changes may be found in another publication.[8]

Fundamentally, therefore, abruptio placentae is characterized by the same pathology as pre-eclampsia and eclampsia. Clinically, it has long been emphasized that abruptio placentae is preceded or accompanied by the symptoms and findings of toxemia in 50 to 80 per cent of the cases. Occasionally, eclampsia and a severe form of abruptio may coexist, and in numerous placentas from cases of pre-eclampsia or eclampsia a minor degree of abruptio may be seen in the form of a firm clot embedded on the maternal surface of the placenta. Trauma plays a very minor role in the etiology of abruptio.

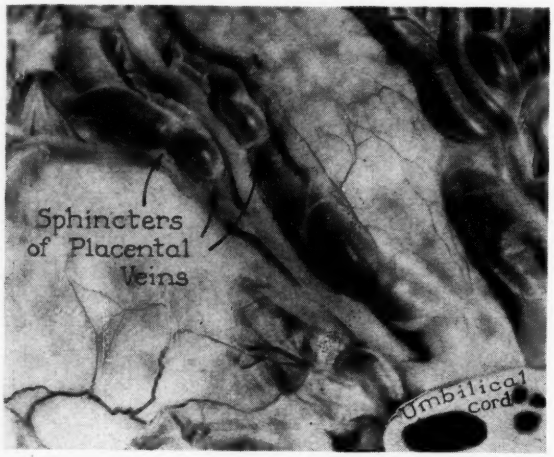


Fig. 8.—Appearance of placental veins on the fetal surface of the placenta, arrows indicating the location of sphincters.

Even though it has been recognized that there exists a very close relation between toxemia and abruptio, there has been no general acceptance of the concept that all cases of abruptio are of a toxemic nature and are based on the same pathology as pre-eclampsia and eclampsia. This is due to the fact that the most severe cases develop in such a fulminating manner that urinary, blood pressure, and clinical findings of toxemia may be completely absent up to the moment of placenta separation and develop only slightly, if at all, in the early days of convalescence.

This apparent paradox is understandable in the light of placental examination. It is in these cases that the most massive, extensive infarction of the placenta is found (Fig. 13). In the fixed and cut specimen, the placental strips appear black throughout one-half, two-thirds, or more of their length. The previously described microscopic pathology is uniformly present in the black infarcted portion (Fig. 14) in marked contrast to adjacent light normal placental tissue.

The manner in which this extensive infarction produces hemorrhage and acute placental separation is conceived to be as follows. Placental tissue possesses a very high content of thromboplastin, an initiator of blood coagulation.[15, 16] An even higher content is found in decidual tissue. The sequence of events in a case of fulminating severe abruptio is apparently as follows:

(1) oxytocic stimulation causing spasm of the spincters of most if not all the placental veins, (2) blockage of venous outflow, (3) distention of villous capillaries, (4) enlargement and crowding of villi, (5) restriction or exclusion of maternal intervillous blood flow, (6) anoxic necrosis of chorionic epithelium, (7) sudden liberation of large amounts of thromboplastin, (8) coagulation of intervillous and subplacental blood, (9) formation of large blood clots in blood lakes at the uteroplacental junction, (10) separation of the placenta and

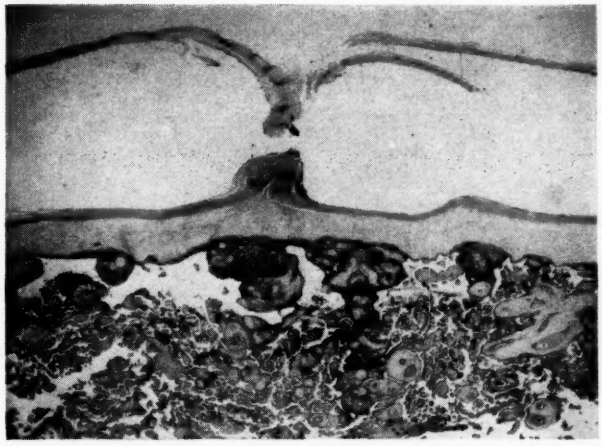


Fig. 9.—Microscopic appearance of sphincter shown in Fig. 8.

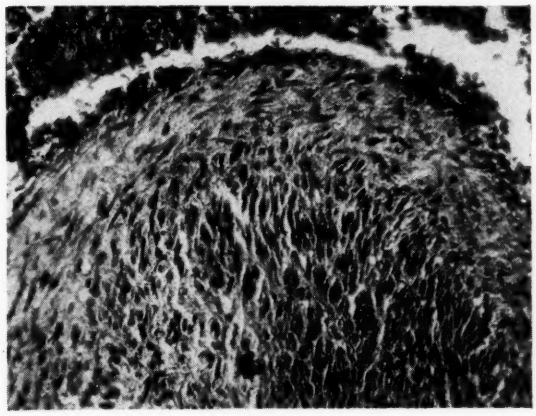


Fig. 10.—High-power magnification of sphincter showing inner longitudinal and outer circular muscle fibers.

intrauterine fetal death, (11) pressure necrosis of the decidua from clots preceding separation, (12) formation of intravascular fibrin thrombi throughout the general circulation from excess thromboplastin, (13) widespread plugging of precapillary vessels with ischemia of tissues and capillary hemorrhages, (14) possible exhaustion of fibrinogen in the blood from excess thromboplastin, with resulting incoagulability of the blood and hemorrhagic tendency.[7, 15, 16]

There seems to be no type of hemorrhage within the body which is characterized by clots of such gross size and firm consistency as are seen in abruptio placentae. Minor degrees of abruptio show recent clots of medium size embedded in the maternal side of the placenta, the clot being superimposed by a layer of acute or subacute infarcted placental tissue from which thromboplastin has been liberated, causing clotting of maternal blood beneath the

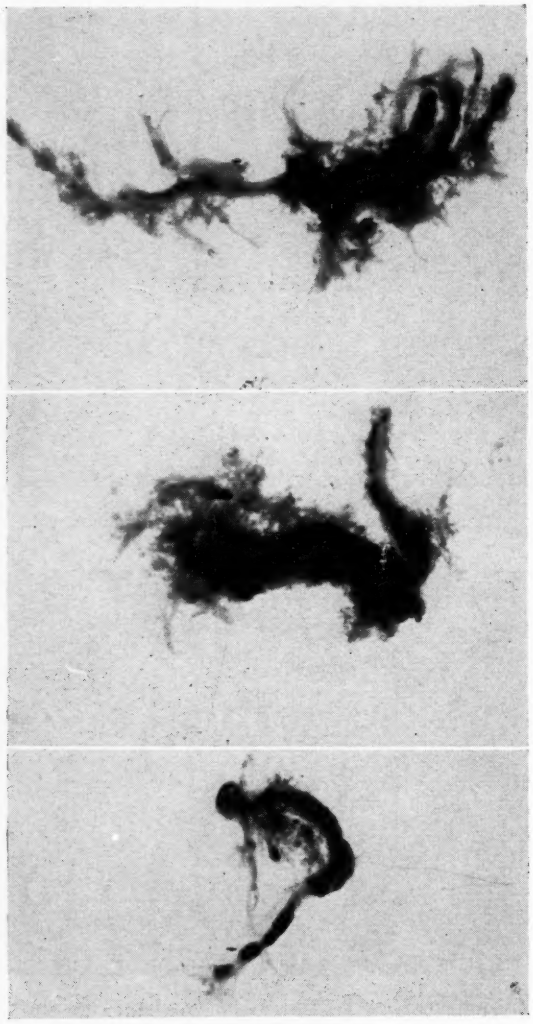


Fig. 11.—Veins dissected from within placental substance, showing beaded appearance, probably due to presence of sphincters (from cleared Vinylite preparation).

local infarction and indenting of the placenta (Fig. 15). It is significant that the infarction appears to be older than the clot. Major degrees of abruptio result from massive acute infarction of most of the placenta, the excessive amount of thromboplastin converting the blood lakes of the entire placental bed into large firm clots. With the evidence of placental infarction antedating the clot formation as seen in many specimens, it does not seem likely that a

lesion of unknown origin in the decidua initiates the sequence of events. It seems more likely that the preceding placental infarction produces the clots which subsequently cause a pressure necrosis of the decidua.

Severe abruptio placentae is therefore a hemorrhagic manifestation of toxemia and represents toxemia in its most severe and fulminating form.[17] The hemorrhagic factor outstrips and takes precedence over the convulsive factor which apparently resides in other and later breakdown products of placental necrosis. Separation of the placenta precludes absorption of the late breakdown products. If sphincter spasm of the placental veins is less severe and less extensive, placental infarction and necrosis progress more slowly and the probable pressor and convulsive effects of breakdown products are more outstanding than the clotting tendency.

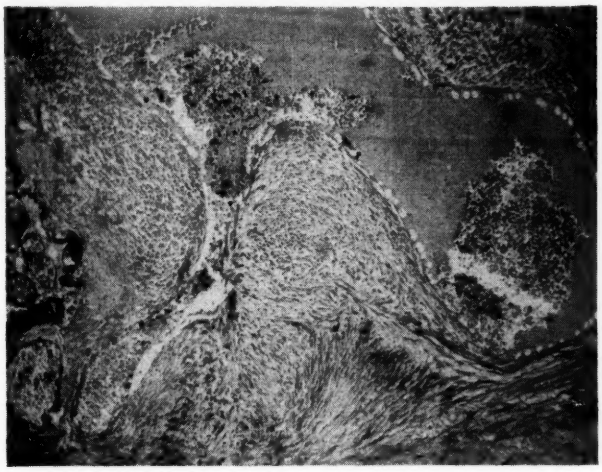


Fig. 12.—Microscopic appearance of a chance section through a venous sphincter in the placental substance.

A much-quoted present-day concept of the cause of placental necrosis postulates general ischemia of the placental bed from maternal vascular disease or atherosclerosis of the decidual arterioles, effects of increased intrauterine pressure, etc. The microscopic appearance of the placental tissue at the junction of the normal and the infarcted areas renders this concept untenable. At the sharply demarcated border, villi and capillaries of normal size, healthy-appearing chorionic epithelium, and open intervillous circulation exist adjacent to crowded, enlarged villi, distended villous capillaries, degenerating chorionic epithelium, and narrowed intervillous circulation.[17] Between the two areas there is no intervening obstacle to maternal intervillous circulation. Furthermore, if one should postulate ischemia of an isolated area of placental tissue by reason of obstruction of a decidual arteriole, maternal blood could still reach this area, since the decidual septa extend not more than two-thirds the distance toward the chorionic plate. The form and extent of the infarction follow the pattern of the fetal circulation and are not generalized throughout the placenta as would be the case if general ischemia of the

placental bed existed. It is difficult to conceive of fulminating abruptio or eclampsia arising from slow-developing processes.

If, as the evidence seems to indicate, abruptio placentae is fundamentally a manifestation of toxemia, it would seem logical to recognize the probability that fulminating toxemia is more likely to eventuate in hemorrhage than in convulsions, the separation of the placenta forestalling the possibility of convulsions except in rare instances.

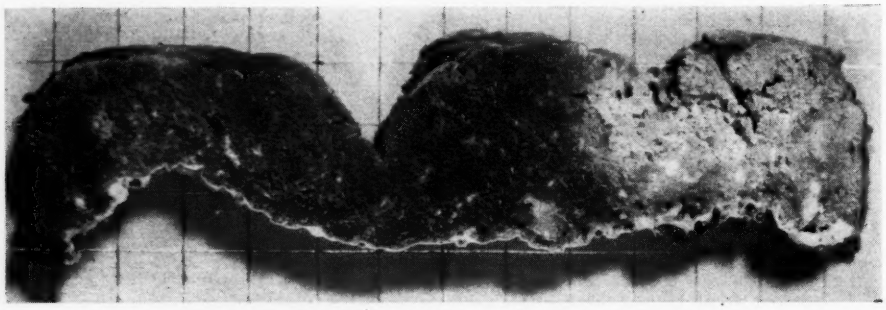


Fig. 13.—Placental strip from a case of abruptio placentae, developing during labor as a fulminating toxemia. Extensive acute (early "E") infarction, involving two-thirds of a succession of strips. The necrosing black and the normal light areas of the placenta are sharply demarcated. Intrauterine fetal death, severe hemorrhage, shock, and complete separation of the placenta ensued. Spontaneous delivery and recovery occurred without development of blood coagulation defects.

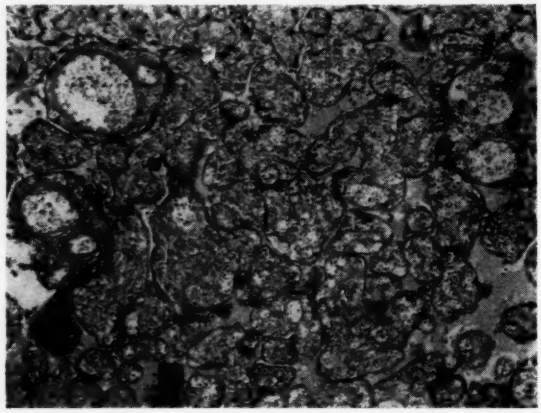


Fig. 14.—Microscopic section from black portion of placental strip (Fig. 13), showing villi enlarged and crowded due to marked dilatation of villous capillaries. Intervillous thrombosis seen, initiated by thromboplastin from early chorionic necrosis. Adjoining lighter placental tissue showed no enlargement of villi or villous capillaries, hence normal intervillous circulation and no necrosis. These findings do not substantiate the concept of placental necrosis from deficiency of the maternal blood supply to the entire placenta.

Bleeding occurred in the third trimester in 105 cases, of which 12 were in the late abortion period (seventh month), 11 premature, in the eighth and the first two weeks of the ninth month, and 82 prelabor, occurring in the last two weeks of the ninth month. The color was red in all cases. There were no macerated or deformed fetuses.

Ruptured marginal sinus was the probable cause in 40 cases; placenta previa in 10 cases; abruptio placentae in 4 cases; trauma (coitus, auto, falls)

in 3 cases, and possibly genital pathology in 8 cases. The cause was unknown in the remaining 40 cases.

While it is difficult to prove, the impression prevails that slight degrees of rupture of the marginal sinus furnish a more plausible explanation of the source of the blood in most, if not all, bleeding of unknown origin. Rupture of the sinus may leave indisputable proof of its previous occurrence in placenta marginata or circumvallata. In other cases, proof lies in scattered fragments or thin layers of puttylike gray or brown fibrin adherent to the membranes. But, in still other cases, the blood from ruptured marginal sinus may channel its way beneath the membranes and escape externally leaving very little if any trace about the placenta or membranes.

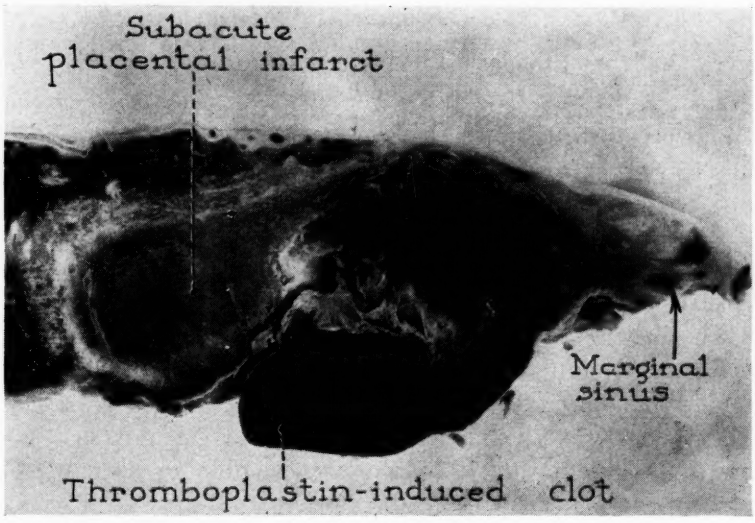


Fig. 15.—Portion of placental strip from a mild case of abruptio placentae, the overlying area of subacute infarction having liberated sufficient thromboplastin to cause clot formation in the deciduoplacental blood lake and mild hemorrhage. The infarction is obviously older than the clot and hence represents the cause and not the effect of hemorrhage. The prognosis for the baby is good in this type.

If bleeding occurs in the first and second trimesters, it apparently has definite prognostic significance as to premature interruption of pregnancy in the third trimester. Among 711 cases of bleeding in the first and/or second trimester(s), premature delivery occurred in 47 cases, or 6.6 per cent. Among

TABLE IV. RELATION OF BLEEDING IN THIRD TRIMESTER (PRIOR TO THAT OF LABOR) TO LATE ABORTION, PREMATURE LABOR, PRELABOR, TYPE OF PRODUCT, AND CAUSE OF BLEEDING

	NO. OF CASES	LATE ABORTION	PREMATURE LABOR	PRELABOR
Bleeding	105	12	11	82
Macerated product	0	0	0	0
Deformed	0	0	0	0
Apparently healthy	100	12	11	77
Cause unknown	40	1	2	37
Ruptured marginal sinus	40	9	6	25
Placenta previa	10	1	1	8
Abruptio placentae	4	1	1	2
Trauma	3	0	0	3
Genital pathology	8	0	1	7

2,186 cases with no bleeding in the first and/or second trimester(s), premature labor occurred in 67 cases, or 3.1 per cent—an incidence less than half as great. This predisposition may possibly be due to the irritating effect of a residue of old fibrin from the previous bleeding.

TABLE V. PROGNOSTIC SIGNIFICANCE OF BLEEDING IN FIRST AND/OR SECOND TRIMESTER TO PREMATURE INTERRUPTION OF PREGNANCY IN THIRD TRIMESTER

	NO. OF CASES	PREMATURE INTERRUPTION OF PREGNANCY IN THIRD TRIMESTER	PERCENTAGE
Bleeders	711	47	6.6
Nonbleeders	2,186	67	3.1

Comment

A survey such as this leaves certain impressions regarding bleeding in pregnancy. In some manner, possibly through assumption of the upright posture, over the ages the human being has become susceptible to hemorrhage as a complication of pregnancy. Under the necessity of providing a rich blood supply to the product of conception, Nature has endowed the chorionic tissue with the capability of eroding its way into decidual blood vessels. In turn, the resistive capability of the decidual layer has been developed to restrict erosive tendency to physiological requirements. The necessity of returning the abundant blood supply to the general circulation has been accomplished by developing an intermediary channel, the marginal sinus, which, by establishing communications with the uterine veins beneath the periphery of the placenta, returns the blood to the general circulation. Weakness in this portion of the temporary blood shunt accounts for most of the bleeding which occurs during an otherwise healthy pregnancy.

Furthermore, Nature's apparent provision against hemorrhage is seen in making the decidua and placenta unusually rich storehouses of thromboplastin, through which the clotting mechanism may be accelerated. At delivery, the interlacing of the uterine muscle fibers provides a ligature-like effect on the sinuses and uterine blood vessels at the placental site, to control bleeding after delivery. Postpartum decidual degeneration adds thromboplastin effect to accelerate thrombosis and provide further protection against hemorrhage.

Imperfections in the natural mechanisms of control over hemorrhage, as well as the effect of excess thromboplastin, which, in case placental necrosis occurs, may go far beyond protective coagulation and become lethal and actually productive of hemorrhage, set up hazards apparently peculiar to the human being and possibly to the primates.

Bleeding occurs most frequently in the first trimester of pregnancy, by a mechanism which is apparently horomonal, related to a blighted state of the product and akin to that by which menstruation occurs. It is much more profuse, however, by reason of the additional source at the placental site where disruption of the deciduoplacental union occurs in the event of abortion. Since the onset is gradual, the initial bleeding is usually brown and the product is usually blighted or absent.

TABLE VI. KNOWN MECHANISMS OF HEMORRHAGE DURING PREGNANCY

1. Hormonal (blighted product)
2. Erosive action of chorionic tissue
3. Rupture of marginal sinus
   A. Circumvallate and marginate placentas
   B. Low-lying, marginal, and partial previas
   C. Idiopathic
4. Pressureless previal area in total previa
5. Biochemical: thromboplastin-induced clotting in abruptio placentae
6. Trauma and genital pathology

Next in frequency in this period of pregnancy is that which is due to a breakthrough and extravasation of blood during the formation of the marginal sinus. Least in frequency is that due to erosive effect of chorionic tissue in the early implantation stage of pregnancy. Pathologic degrees of chorionic erosion are seen in hydatidiform mole, chorionepithelioma, and ectopic pregnancy. Minor and infrequent causes of bleeding may be genital pathology such as cervical polyp and erosion, also trauma from coitus, falls, and accidents. These are discoverable at, and common to, any stage of pregnancy.

Bleeding in the second trimester is more likely to be initially red and a conceptus of some degree of development more likely to be present, although frequently blighted. The mechanism of bleeding is still predominantly hormonal, but other mechanisms, concerned with marginal sinus rupture, low implantation, or necrosis of placental tissue are more frequently responsible.

In the third trimester the hormonal mechanism plays a minor role. Low implantation of the placenta and greater stretch and strain on the membranes predispose to rupture of the marginal sinus, which is more frequently seen. If total placenta previa is present, the mechanism of bleeding concerns the vacuum of blood pressure in the previal portion of the placenta, which induces the subchorionic-plate blood stream to descend into the pressureless previal area as hemorrhage. The placental findings favor these mechanisms of bleeding rather than disruption of the deciduoplacental attachment around the internal os.

The mechanism of bleeding in abruptio placentae is apparently biochemical. By a sequence of events described in the context, the occurrence of placental necrosis liberates a large amount of thromboplastin which induces clotting in the blood lakes underlying the placenta. Extremely large clots are formed, which cause complete or partial separation of the placenta. The placental pathology associated with this phenomenon is identical with that peculiar to pre-eclampsia and eclampsia, only more extensive. The evidence indicates that abruptio is a hemorrhagic manifestation of toxemia of pregnancy.

Since many patients bleed in more than one trimester of pregnancy, the sum of the number of bleeders in each trimester is greater than the number of patients who bled during pregnancy.

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Discussion

DR. ROBERT A. KIMBROUGH, JR., Philadelphia, Pa.—Too many of us, being content with the successful clinical management of our urgent cases of bleeding in pregnancy, have neglected the opportunity to study the placental abnormalities which gave rise to the complication. The essayists have told us repeatedly of their findings and interpretations and I, for one, feel guilty that I have not followed their methods of fixation and study. For this reason alone, there exists serious doubt concerning my qualification for this discussion.

Several practical considerations deserve emphasis. First, the fact that one-third of 3,125 consecutive patients bled during pregnancy is worthy of note. Second, 6 per cent (200 patients) had implantation bleeding at the time of the first missed period; of these, only 3.5 per cent aborted. These figures speak loudly against attributing continuation of pregnancy to any mode of treatment of threatened abortion. Third, the essayists have postulated from their study that initial brown bleeding following the first missed period is more likely to be followed by abortion than is bright red initial bleeding, the former being attributed to absence of or defect of the conceptus, and the latter to a break in the placental blood shunt. Perhaps our therapeutic zeal, therefore, should be expended only upon those patients who have initial bright red bleeding in the first trimester.

Although the existence of the marginal sinus has been known since Jacquemier first wrote of it in 1839, little clinical importance has been attached to it in this country. Indeed, many of our much-quoted texts do not mention it. In a recent survey, Dr. Bartholomew and his group attributed 43 per cent of bleeding in the third trimester to rupture of the marginal sinus. In the light of this finding, I am embarrassed to admit that I have yet to make this diagnosis preoperatively.

All of us have had the experience of performing cesarean sections for profuse painless bleeding in late pregnancy with a diagnosis of placenta previa only to find the placenta normally situated. Such hemorrhages must be due almost invariably to rupture of the extremely vulnerable marginal sinus; indeed, when one sees the thinness of the wall of the marginal sinus and thinks of the trauma to which these walls are subjected in every pregnancy and labor, one wonders that rupture does not occur almost routinely. Such accidents clearly explain profuse painless bleeding in late pregnancy from the normally located placenta.

Wide adoption of the expectant treatment of placenta previa and rupture of the marginal sinus have allowed the natural progress of pregnancy and labor to resolve these problems along more simple methods of management. Mild hemorrhages which cease and do not recur are

more likely to be due to rupture of the sinus. Recurring hemorrhages of increasing severity are probably attributable to placenta previa. The condition of the cervix at the time at which delivery becomes mandatory remains the chief criterion of procedure.

The idea that rupture of the marginal sinus constitutes a mechanism of bleeding in partial and low-lying placenta previa is logical. In addition, may there not be also an actual separation of the placenta from the decidua? Of this I am certain.

With Dr. Bartholomew's well-known concept of the sequence of events in the placenta in cases of toxemia and abruption I am not qualified to disagree. It is logical, and his illustrations are indeed convincing. As Agrippa said to St. Paul in Holy Writ, "Almost thou persuadest me . . ."

DR. BARTHOLOMEW (Closing).—I regret that lack of time necessitated the omission of the mechanism of bleeding in abruptio placentae. In making a survey such as this, it is interesting to note the remarkable adaptations Nature makes to control these situations and prevent bleeding. Concerning the possibility of hemorrhage from abruptio in the late months of pregnancy, Nature apparently makes of the placenta a storehouse of thromboplastin which must very appreciably lessen the amount of bleeding since it accelerates clotting. Excessive release of thromboplastin can go to dangerous lengths and cause widespread coagulation of the blood, as has been reported by Schneider. To control the bleeding which comes at the time of delivery there is available the remarkable effect of the ligature-like constriction of the sinuses by the muscular elements of the uterine wall, which is another remarkable adaptation to prevent bleeding. It is strange that the human being is so subject to bleeding; I understand from veterinarians that this does not occur among animals. As stated in the paper, I communicated with a laboratory in Jacksonville where chimpanzees are studied and it is found that they are not entirely free from bleeding. They show implantation bleeding and occasionally have copious hemorrhage in the latter part of pregnancy which is much like abruptio.

DOES THE ADMINISTRATION OF DIETHYLSTILBESTROL DURING PREGNANCY HAVE THERAPEUTIC VALUE?*†

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In 1946 Smith and Smith[1] suggested that increasing amounts of diethylstilbestrol should be administered to all women during pregnancy to prevent or decrease the hazards of the late complications of pregnancy for mothers and babies. The basis for such prophylactic therapy as well as the active therapy of these pregnancy complications stems from a series of experiments by the Smiths on the steroid hormones in normal and abnormal pregnancy.[2] These laboratory observations and their theoretical implications were supported by clinical observations, part of which were made under the supervision of the Smiths and part were the collected reports of other clinical observers.

The use of diethylstilbestrol to prevent and to treat pregnancy complications is based on the supposition that there develops a deficiency in the production of progesterone and other steroids by the placenta which predisposes to or causes these pregnancy complications. The secretion of these steroids can be stimulated by diethylstilbestrol. The increased amounts of steroids made available by the placenta postpone, reduce the severity of, or prevent some of the late complications of pregnancy.

The laboratory experiments which provided the background for this interesting concept of the Smiths have lacked confirmation by other investigators. Davis and Fugo[3, 4] in two reports noted that the administration of diethylstilbestrol to patients during pregnancy did not result in an increased output of urinary pregnanediol, a measure of progesterone metabolism. Sommerville, Marrian and Clayton[5] confirmed these observations and noted a drop in urinary pregnanediol and no gross change in endogenous estrogen. Although many additional experimental data will be necessary to determine the role of diethylstilbestrol in placental steroid metabolism, this paper will confine itself to the clinical implications of the Smith concept.

Smith and Smith in 1949[6] reported on the influence of diethylstilbestrol on the progress and outcome of pregnancy in a series of primigravidas. As

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controls they used a series of primigravidas who received no special treatment. They recorded the following conclusions: (1) It decreased the incidence of the late toxemias of pregnancy. (2) The premature infants born were unusually large for their gestational age. (3) The incidence of postmaturity was decreased. (4) The incidence of unexplained stillbirths was apparently decreased. (5) The neonatal death rate was decreased.

The most serious criticism of this study is the lack of adequate controls. Patients to whom trial medication is administered inevitably receive more meticulous study and medical care than other patients cared for simultaneously. In two nutrition studies conducted by Dieckmann and associates[7] patients who were cooperative and sufficiently intelligent to follow the dietary instructions, keep good records, and attend clinic regularly had a lower incidence of abortion, premature delivery, pre-eclampsia and eclampsia, as well as a lower perinatal death rate, when compared with those of similar groups of women delivered concurrently at this hospital. However, when these figures were compared with those obtained in a control group in which the women received identical treatment with those on the nutrition study there were no significant differences.

The prophylactic administration of diethylstilbestrol and its therapeutic use in pregnancy complications have created widespread interest. To prevent, to postpone, or to ameliorate some of the common hazards of childbirth for mothers and babies is certainly a worthy goal. That all this can be accomplished by the daily consumption of a few tablets is indeed enticing. However, a careful perusal of the literature reveals that most of the clinical data are not supported by adequate controls.[8, 9]

The properly conducted clinical trial demands (1) that patients and staff should have no knowledge of the medication on trial; (2) that a similar group of patients should receive placebo medication which is not discernible from the medication on trial; and (3) that the two groups of patients must be treated simultaneously and as nearly alike as possible. In only one study recently reported by Ferguson[10] have these criteria been met. He concluded that diethylstilbestrol had no effect on the incidence of pre-eclampsia, prematurity, perinatal mortality, fetal weight, and size of the placenta.

We felt that it was timely to conduct a strictly scientifically controlled clinical experiment to determine the value of diethylstilbestrol in our obstetric practice. The first patient was admitted to this study on Sept. 29, 1950. The study terminated Nov. 20, 1952.

The following criteria were used: The sampling was to be sufficiently large so that the results would be statistically significant. A control group of patients who were managed similarly and simultaneously was necessary. It was decided that 2,000 patients registered consecutively in our prenatal clinics prior to the twentieth week of gestation would provide an adequate number. Every other patient would serve as a control. In order to eliminate the personal element, each patient was assigned a code number known only to one individual who was not a clinician. The identity of the two groups was not

available until after the data were tabulated by the statistician. A study sheet in duplicate containing pertinent information and the dosage schedule was kept for each patient. One copy was retained in the prenatal record and the other was in the patient's possession so that she could record the daily dosage of tablets.

Four different tablets were designed for this experiment, tablets containing 5 and 25 mg. of diethylstilbestrol and similar tablets containing a placebo. Incorporated in all the tablets was 3 mg. of phenol red, an easy tracer substance. This dye is eliminated in the urine and each urine sample was checked for its presence in order to ascertain if the patient was taking her tablets. She was not aware of this check and some women were eliminated from the study because their urine samples consistently contained no dye.

The following schedule for the administration of tablets was followed: The initial dose varied from 5 to 37.5 mg., depending on the period in the gestation when the patient registered in our clinic. The maximum daily dose of 150 mg. was administered during the thirty-fourth and thirty-fifth weeks of the pregnancy. The duration of the pregnancy was calculated from the menstrual data. The 25 mg. tablets containing stilbestrol or the placebo were scored so that they could easily be broken in half and only one-half consumed.

Each patient was instructed as to the beginning dose and the continuing amounts to be taken. She was asked to note each daily dose on the printed schedule, thereby providing her with a constant reminder to take her medication. At each prenatal visit this schedule was reviewed with her and a notation made as to the degree of patient cooperation. When she completed her medication at the end of the thirty-fifth week, she returned the remaining tablets and her medication chart.

Every patient on registering in our prenatal clinics who was thought to be pregnant between 6 to 20 weeks, inclusive, was offered a box of tablets without charge. Included were women who were known to have complications such as chronic hypertensive vascular disease, diabetes mellitus, or repeated abortions. Each patient was told that previous reports indicated that the tablets were of value in preventing some of the complications of pregnancy and that they would cause no harm to her or the fetus. No coercion was used but she was asked to return the tablets if she did not wish to cooperate. No special clinics or procedures were instituted.

She was instructed to save the urine from bedtime to the next morning on the day of her routine clinic visit and bring in a small specimen. It was tested for phenol red by alkalinizing with 10 per cent sodium hydroxide. A red color merely indicated that the patient had taken one or more of the stilbestrol or placebo tablets. We could not determine how many tablets she took per day or week because of the individual differences in absorption and excretion of phenol red. The amount of this dye was such that a few patients tested negative in periods when they were taking only one pill; all tested positive with two or more tablets. In the patient who was taking the pills regularly whose urine was tested at fairly frequent clinic visits starting at 7

weeks, the sequence of expected test reports was negative-positive, positive, negative-positive when the switch to 25 mg. pills was made, and then positive until administration was discontinued. In general, the reports based on testing for phenol red correlated well with those based on the patient's statements to the clinic staff.

Each set of boxes of pills carried a label with the number which was to be assigned to the patient taking that particular batch of pills. The numbers ran consecutively. Approximately equal numbers of stilbestrol and placebo pills were given out during the period of the study. When the pills were given out to the patient, the number on the boxes was assigned to her and recorded in the record and on the two medication sheets. The patient's name, unit number, and study number were listed in a book kept by the clinic staff.

R. E. P. packaged all the tablets, kept records of the number of boxes sent out, and was the only person who knew the code numbers which he placed in a sealed envelope. At the completion of the study, the sealed envelope containing the code was opened in the presence of three people, the numbers checked with R. E. P., and found to be correct. Because there was a difference in our results from those reported by the Smiths, we wished to determine if there had been a mix-up in the stilbestrol and placebo tablets, which were identical. A representative from Eli Lilly and Company selected tablets from each of the containers and sent them to his company for analysis. Their report states that the tablets marked "stilbestrol" contained the substance in the proper amounts. A colorimetric test for stilbestrol in our laboratory was positive for the same batch of tablets designated "stilbestrol."

The statistician, who had considerable experience with medical charts in our specialty, coded all the pertinent data from the patient's record on IBM cards. W. J. D. served as her consultant when any question arose concerning the interpretation of factual data in the record. He did not know which tablets had been taken by the patient.

A large number of data were accumulated in this study. They concern the reproductive histories of 1,646 mothers and their babies cared for in a teaching institution and the beneficiaries of present-day obstetrical care. This report will concern itself only with some of the questions that have been raised by the ever-increasing use of diethylstilbestrol in obstetrics.

A total of 2,162 patients were entered in this study, evenly divided between those who received stilbestrol and those who received placebos. When the final data were tabulated there remained 1,646 suitable records. Thus 22 per cent of women to whom tablets were given were dropped from the study.

In brief, women were dropped from our study for the following reasons: (a) 125 women cancelled their reservations because they moved or delivered elsewhere; (b) 198 women did not take the tablets regularly according to schedule; (c) 52 women aborted prior to the end of 21 days of medication; (d) the remainder were dropped because of such reasons as not pregnant, husband objected to medication, nausea, etc.

The data presented in the following discussion and tables concern 840 patients who took graduated amounts of diethylstilbestrol according to the

schedule in Table I suggested by the Smiths, beginning prior to the twentieth week and continuing uninterruptedly for at least 5 weeks. Serving as controls were 806 women who took similar tablets according to the same schedule containing only a placebo and the dye and cared for simultaneously by the same medical staff under similar conditions. The statistician and the clinicians are in agreement that these two groups of patients are comparable and can be treated as such.

TABLE I. DAILY DOSAGE OF DIETHYLSTILBESTROL

WEEKS PREGNANT	DIETHYLSTILBESTROL
7-8	5 mg.
9-10	10 mg.
11-12	15 mg.
13-14	20 mg.
15-16	25 mg.
17, 18 and 19	37.5 mg.
20-21	50 mg.
22-23	67.5 mg.
24-25	75 mg.
26-27	87.5 mg.
28-29	100 mg.
30-31	112.5 mg.
32-33	125 mg.
34-35	150 mg.

The distribution of patients in the two groups can be noted in Table II. It is entirely accidental that the several categories of patients are so evenly divided between those who received diethylstilbestrol and those in the control group to whom a placebo was administered. The term primigravida is used in our data to indicate the first pregnancy. If the patient has had one or more additional pregnancies which terminated prior to viability she is considered a primipara in the current pregnancy studied. If she has had one or more viable babies prior to the current pregnancy she is classified as a multipara.

TABLE II. DISTRIBUTION OF CASES BY HISTORY

	STILBESTROL		CONTROL	
	NO.	%	NO.	%
Primigravidas	314	37.4	316	39.2
Gravida ii (1 abortion)	103	12.3	91	12.8
Gravida iii (2 abortions)	19	2.3	18	2.2
Gravida iv (3 abortions)	9	1.1	8	1.0
Gravida v (4 abortions)	1	.1	0	–
Multiparas, normal	287	34.1	284	35.2
Multiparas with abortion and other abnormalities	36	4.3	25	4.5
Multiparas, abnormal, no abortion	71	8.5	64	7.9
Total	840		806	
All primiparas	446		433	
All multiparas	394		373	

Fig. 1 is a graphic distribution of the period in gestation when the patients in this study began to take tablets. Forty-one per cent of the women began to take stilbestrol prior to the eleventh week compared to 43 per cent

of the controls; 43 per cent of each group started medication prior to the fifteenth week of the gestation; 14.4 per cent of the stilbestrol group and 11.8 per cent of the controls began prior to the nineteenth week. The average time of the patient's entry into the study was 11.5 weeks for the primiparas and 12.5 weeks for the multiparas.

In the experimental statistical approach to a clinical problem it is important to compare similar groups of patients in so far as human material will allow. Table III records the mean figures for age, height, and weight increment during pregnancy of the stilbestrol-treated group and the control group. It is surprising how closely these groups compare with each other. The multiparas averaged about three years older than the primiparas. The initial mean weights of the two groups were almost similar. The total weight gain during pregnancy in the primiparas was 9.8 kilograms, compared with 9.5 kilograms in the controls; 9.3 kilograms in the multiparas, compared with 8.7 kilograms for the controls. There was very little difference in their weight loss by the tenth postpartum day.

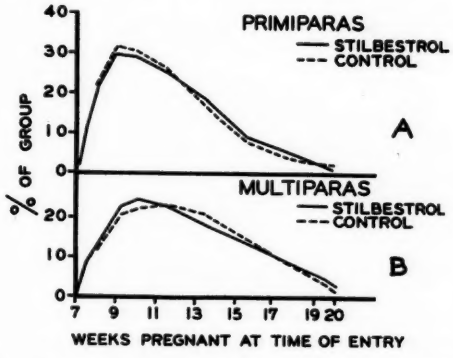

Fig. 1.—Shows the distribution of times of entry to study.

The duration of pregnancy is the most important factor in prematurity. The several criteria for calculating the length of gestation have wide limits of error. It is usually agreed that the menstrual data provide the most simple and probably the most accurate means of calculating the due date. Using the first day of the last normal menstrual period to determine the expected delivery date, the mean length of pregnancy was 38.7 weeks in the primiparas on stilbestrol medication and 39.3 weeks in the controls; 38.6 weeks in the multiparas on stilbestrol and 39.4 weeks in their controls. Analysis of the length of pregnancy for all cases shows a statistically significant longer duration of pregnancy for both control primiparas and multiparas, at the $P = 0.01$ level. Statistical analysis of the uncorrected data shows that stilbestrol did shorten the duration of the pregnancy before the thirty-seventh week, as shown in Table IV. It is obvious that there is a marked increase in the number of primiparas and multiparas in the stilbestrol group over that of the control group up to 37 weeks. These data seem to indicate that stilbestrol favors premature labor. It may be due to an excess amount of hormone. If the patient reaches 37 or more weeks of gestation, the previous administration

of stilbestrol has no further effect, but before that time it appears to change the balance in that more patients deliver prematurely. Data corrected to compare with the Smiths' are shown in Fig. 4.

TABLE III. AGE, HEIGHT, WEIGHT, AND DURATION OF PREGNANCY (MEAN FIGURES)

	STILBESTROL GROUP		CONTROL GROUP	
	PRIMIPARAS	MULTIPARAS	PRIMIPARAS	MULTIPARAS
Age (years)	26.7	29.5	26.4	29.0
Height (cm.)	162.2	162.0	162.2	161.5
Weight (kilograms, minimum)	57.9	59.8	58.5	59.5
Weight gain	9.8	9.3	9.5	8.7
Weight loss in puerperium	7.4	7.2	7.7	7.5
Length of gestation (weeks) (Term 40 weeks)	38.7	38.6	39.3	39.4

TABLE IV. TIME OF DELIVERY BASED ON DATE OF LAST MENSTRUATION

WEEKS' GESTATION	PRIMIPARAS		MULTIPARAS	
	STILBESTROL	CONTROL	STILBESTROL	CONTROL
29-36	5.1%	3.6%	8.4%	4.9%
37-42	89.8%	92.2%	88.3%	88.5%
43 and over	5.1%	4.2%	3.3%	6.6%

TABLE V. TOXEMIAS OF PREGNANCY

	PRIMIPARAS				MULTIPARAS			
	STILBESTROL		CONTROL		STILBESTROL		CONTROL	
	NO.	%*	NO.	%*	NO.	%*	NO.	%*
Pre-eclampsia-eclampsia	16	3.5	13	3.0	1	0.3	3	0.8
Essential hypertension	11	2.5	6	1.4	11	2.8	10	2.7
Chronic glomerulo-nephritis	2	0.4	1	0.2	3	0.8	0	--
Pyelonephritis	0	--	0	--	1	0.3	0	--
Abruptio placentae	3	0.7	2	0.5	2	0.5	3	0.8
Total	446	(840)	433		394	(806)	373	

*Percentage of group.

TABLE VI. WEIGHT OF BABIES

	PRIMIPARAS				MULTIPARAS			
	STILBESTROL		CONTROL		STILBESTROL		CONTROL	
WEIGHT IN GRAMS	NO.	%	NO.	%	NO.	%	NO.	%
1,000-1,299	3	0.7	1	0.2	4	1.1	2	0.6
1,300-2,499	29	6.8	16	3.8	23	6.1	17	4.8
2,500-4,499	387	91.7	400	95.5	342	90.9	332	93.2
4,500 and over	3	0.7	2	0.5	7	1.9	5	1.4
Total cases	422		419		376		356	
Average weight all babies	3,200		3,300		3,300		3,300	
Average weight of babies 2,500 grams and over	3,300		3,360		3,407		3,395	

Abortion.—During the last five years the incidence of abortion (1 to 999 grams or before the twenty-eighth week) was 8.3 per cent. The data in Fig. 2 exhibit the incidence of abortion among the several groups of patients

studied. Abortions occurred in 4.7 per cent of primiparas on stilbestrol, compared with 2.5 per cent of the controls; in 3.3 per cent of the multiparas on stilbestrol, compared with 1.6 per cent of the controls. Although the abortion rate in the stilbestrol group was higher than in the control group, the total number of patients was too small to be statistically significant. Since most abortions occur before the seventeenth week, and since patients were omitted if they had less than 5 weeks of treatment, it is obvious why the abortion rate was lower than the hospital incidence.

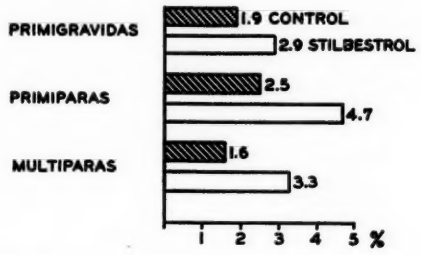

Fig. 2.—Depicts the incidence of abortion (fetuses weighing 1 to 999 grams).

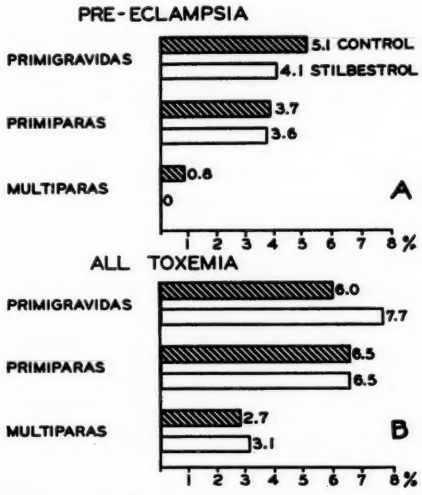

Fig. 3.—*A*, The incidence of pre-eclampsia. *B*, The incidence of pre-eclampsia and hypertensive disease in the various groups of patients.

Toxemias of Pregnancy.—In Table V are listed all of the patients who exhibited clinical findings which warranted the diagnosis of toxemia of pregnancy. It will be noted that the incidence of pre-eclampsia was 3.5 per cent in the primiparas on stilbestrol compared to 3 per cent in the control group; 0.3 per cent in the multiparas compared with 0.8 per cent in the controls. The incidence of essential hypertension was 2.5 per cent in the primiparas on stilbestrol in contrast to 1.4 per cent in the controls; it was 2.8 per cent in the multiparas compared with 2.7 per cent in the controls.

Fig. 3 presents a graphic distribution of the toxemia patients after the histories were carefully reviewed by Dieckmann and corrected to conform

TABLE VII. INCIDENCE OF PREMATURES BY WEIGHT
(PERCENTAGE OF CASES)

WEIGHT OF BABY	UNDER 1,500 GRAMS		1,500-1,999 GRAMS		2,000-2,499 GRAMS		TOTALS	
	STILBESTROL	CONTROL	STILBESTROL	CONTROL	STILBESTROL	CONTROL	STILBESTROL	CONTROL
Primigravidas	1.9	.6	2.2	1.9	4.1	2.5	8.3	5.1
Other primiparas	2.3	--	.8	--	5.3	4.3	8.3	4.3
Multiparas, normal	3.8	1.8	.3	.4	3.5	2.8	7.7	4.9
Multiparas with abortion and other abnormalities	5.5	4.0	2.8	8.0	5.5	16.0	13.9	28.0
Multiparas, abnormal, no abortions	8.4	1.6	2.8	--	2.8	7.8	14.1	9.4
All primiparas	2.0	.5	1.8	1.4	4.5	3.0	8.3	4.8
All multiparas	4.8	1.9	1.0	.8	3.6	4.6	9.4	7.2
All cases	3.3	1.1	1.4	1.1	4.0	3.7	8.8	6.0

to the data presented by the Smiths. These corrected results differ very little from the uncorrected data in Table V. The several groups were too small to treat statistically. However, not only did the administration of diethylstilbestrol fail to decrease the incidence of toxemias but there was no difference in the time of onset of this complication nor in its severity in the two groups of patients studied. One must conclude that the prophylactic administration of stilbestrol has no therapeutic value in decreasing the hazards of late pregnancy toxemias.

Birth Weights of Babies.—In Table VI are listed all of the babies according to their birth weights. It is obvious that in the various weight categories there was a slightly greater percentage of babies that weighed less in the stilbestrol group as compared with those in the control group in both primiparas and multiparas. The average weight of all babies of primiparas on stilbestrol was 3,200 grams compared with 3,300 grams for the controls; the babies of multiparas on stilbestrol, as well as those on placebos, averaged 3,300 grams.

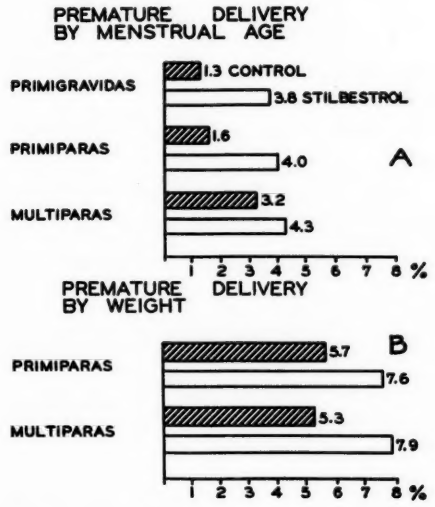

Fig. 4.—*A*, The incidence of premature babies by menstrual age. *B*, By weight of the babies.

Prematurity.—The diagnosis of prematurity is based on the weight, length of the gestation, and physical findings of the baby. The duration of pregnancy is not easy to determine accurately, for it is subject to wide variation. The physical signs of prematurity, including x-ray study of ossification centers, are not reliable indices, nor do they provide sharp end points. Weight is the most reliable criterion for prematurity. During the past five years the over-all incidence of premature delivery based on babies weighing 1,000 to 2,499 grams was 6.6 per cent. Table VII lists the incidence of prematurity by weight. In the group of women on stilbestrol, 8.8 per cent of the babies weighed less than 2,500 grams compared with 6 per cent in the control group. In the stilbestrol group 3.3 per cent weighed under 1,500 grams, 1.4 per cent weighed 1,500 to 1,999 grams, and 4 per cent weighed 2,000 to 2,499 grams. This compares with 1.1 per cent, 1.1 per cent, and 3.7 per cent in the control group.

Fig. 4 is a graphic presentation of the data on premature babies corrected to conform to the data presented by the Smiths by omitting women with known hypertension, diabetes mellitus, chronic nephritis, twins, etc. In *A* the premature babies are classified by menstrual age and in *B* by weight. It is obvious that using either criterion for prematurity, a greater number of premature babies were delivered to women to whom stilbestrol was administered as compared with the control group.

Premature infants of mothers who took stilbestrol did not appear to differ from those of the control mothers at the same gestational age. If prematurity was defined in terms of weight of the baby, the incidence was higher, but not significantly so, for all stilbestrol groups. On the basis of week of delivery, there was a real difference between stilbestrol and control cases. Both primiparas and multiparas tended, with fair statistical significance, to deliver earlier in the stilbestrol groups, and the primiparas who took stilbestrol delivered a significantly larger number of infants before the thirty-eighth week.

Postmaturity.—This is exceedingly difficult to define. The menstrual data are so unreliable that they are of little value in determining postmaturity. Undoubtedly, the size of the baby need not bear a direct relationship to his maturity. In our data, Table IV, delivery occurred at an estimated 43 weeks or longer in 5.1 per cent of the primiparas on stilbestrol compared to 4.2 per cent of the controls. The figures for multiparas were 3.3 per cent and 6.6 per cent, respectively. In Table VI the number of babies that weighed more than 4,500 grams is comparable in the several groups of patients. The administration of stilbestrol did not prevent postmaturity.

TABLE VIII. PERINATAL MORTALITY
(ALL DEATHS OF FETUSES 1,000 GRAMS AND OVER)

	PRIMIPARAS		MULTIPARAS	
	STILBESTROL	CONTROL	STILBESTROL	CONTROL
Stillbirths:				
Antepartum, under 24 hours	0	2	0	1
Antepartum, more than 24 hours	4	0	2	1
Intrapartum	1	2	0	2
Total stillbirths	5 (1.1%)	4 (0.9%)	2 (0.5%)	4 (1.1%)
Neonatal:				
Under 24 hours	2	0	5	2
1-10 days	5	0	4	1
Over 10 days	0	1	0	0
Total neonatal	7 (1.6%)	1 (0.2%)	9 (2.3%)	3 (0.8%)
Perinatal	12 (2.7%)	5 (1.1%)	11 (2.8%)	7 (1.9%)

The pediatricians who studied our babies could find no differences in the strength, vigor, nursing ability, weight loss, and other criteria of growth and development in babies born of mothers who had received stilbestrol and those who had taken placebos. There were no statistically significant differences in the length of babies in these two groups. It must be concluded that the pro-

phylactic administration of diethylstilbestrol to mothers did not decrease the incidence of prematurity based on fetal weight nor did it result in larger babies for their gestational age.

Perinatal mortality includes all stillbirths and neonatal deaths of babies weighing 1,000 grams or more. From 1946 to 1952 the incidence of stillbirths was 0.95 per cent and of neonatal deaths was 1.06 per cent. Data for this study are given in Table VIII. The stillbirth rate in primiparas on stilbestrol was 1.1 per cent compared with 0.9 per cent in the control group; in multiparas it was 0.5 per cent compared to 1.1 per cent. The neonatal death rate of infants born to primiparas on stilbestrol was 1.6 per cent compared to 0.2 per cent in the control group; in multiparas it was 2.3 per cent compared to 0.8 per cent in the controls. The perinatal mortality was 2.7 per cent in all the women who were taking stilbestrol compared to 1.5 per cent in the women in the control group.

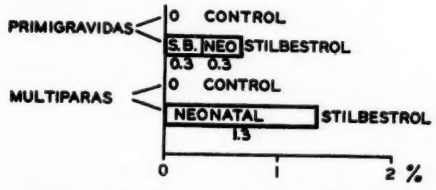

Fig. 5.—Shows the stillbirth and neonatal death rates (1,000 or more grams) for the various groups of patients.

Fig. 5 is a graphic presentation of perinatal mortality after the data were corrected by the deletion of patients with known essential hypertension, diabetes mellitus, chronic glomerular nephritis, etc., to conform to the data presented by the Smiths. Although the sizes of the groups are too small to have statistical significance it is apparent that all the fetal deaths occurred in infants of the women who received stilbestrol.

Our data on perinatal mortality do not indicate that the prophylactic administration of diethylstilbestrol influenced favorably the fetal salvage.

Congenital Anomalies.—All anomalies present in the babies at birth are listed in Table IX. It will be noted that most of these are minor and of no great importance. However, it is obvious that there are no differences between the two groups of patients. It can be concluded that diethylstilbestrol did not increase or decrease the occurrence of fetal anomalies.

Nausea and Vomiting.—The ability of the pregnant patient to consume huge amounts of diethylstilbestrol without nausea or vomiting is an old observation. In our data, 15 women (1.4 per cent of the original group) discontinued stilbestrol because of nausea or vomiting. However, 16 women (1.5 per cent of the original group) who were taking placebos stopped the tablets for the same reason. All of those dropping out because of nausea specifically reported that the pills made them sick, and many stated that the nausea decreased sharply as soon as they stopped. Yet half of these women were actually taking placebos.

Since our data were at variance with those of the Smiths, they were all rechecked. The charts of patients with toxemia of pregnancy, premature delivery, stillbirths and neonatal deaths, and any other complication or abnormality, were examined again by one of the senior authors with no knowledge of the kind of medication. There was no significant change in any of the results.

TABLE IX. CONGENITAL ANOMALIES

TYPE OF ANOMALY	PRIMIPARAS		MULTIPARAS	
	STILBESTROL	CONTROL	STILBESTROL	CONTROL
Minor	7	7	9	4
Skin, as papilloma	7	12	7	6
Cystocele, hydrocele	4	3	3	2
Harelip, cleft palate, etc.	1	0	0	1
Clubfeet, multiple digits	2	5	6	2
Mongolism	0	0	0	1
Brain and spinal cord	1	0	0	0
Cardiac, etc.	2	1	1	2
Gastrointestinal	1	0	0	0
Genitourinary	0	2	0	3
Multiple major	2	2	1	3
Total anomalies	27	32	27	24
Total infants	426	415	376	361

Conclusions

A strictly controlled clinical trial of the therapeutic value of diethylstilbestrol administered to patients during pregnancy in reducing the hazards of some of the late complications of pregnancy for mothers and babies has been reported.

The various complications were studied in the total unselected group of patients divided into primigravidas, primiparas, and multiparas. Then the groups were again studied after all groups were corrected to compare with the Smiths'.

The results of the administration of diethylstilbestrol in graduated amounts to 840 patients according to a schedule suggested by the Smiths were compared with the results of an identical placebo tablet given to 806 patients. Stilbestrol did not reduce the incidence of abortion, prematurity, or postmaturity. Premature babies of stilbestrol-treated mothers were no longer nor more mature for their gestational ages than comparable prematures in the control group of placebo-treated mothers. It did not decrease the incidence of perinatal mortality. It did not decrease the frequency of the toxemias of pregnancy.

Acknowledgment is made to Eli Lilly and Company for aid in making the stilbestrol and placebo tablets with the dye and for the final determination of the stilbestrol; to Lillian Natusko for the examination of the urines for phenol red; to the staff and residents for their cooperation.

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Discussion

DR. GEORGE van S. SMITH, Brookline, Mass.—I realize how disappointed Dr. Dieckmann and his associates must be at getting negative results after putting so much thought, work, and expense into their carefully planned and well-carried-out experiment. When he told us he was going to run this experiment, we were confident that he would gain evidence for a beneficial effect of stilbestrol, although we had misgivings as to whether therapeutic value could be really demonstrated in the number of heterogeneous pregnancies he was planning to analyze. When our experiment was being organized early in 1947, Dr. Jane Worcester, Assistant Professor of Biostatistics at the Harvard School of Public Health, who had had considerable experience in the analysis of nutritional studies during pregnancy, stated that unless treated and control groups were as homogeneous as possible, thousands of each would have to be studied to give any conclusive evaluation of therapy. She advised that the experiment be limited to normal primigravidas who at the start had every reason to expect normal pregnancies. This we did, with beneficial results in the treated group which were significant. The negative results just reported and those recently published by Dr. Ferguson mean to us that not enough heterogeneous pregnancies were studied. To break down such a series into truly comparable categories is difficult, if not impossible. Their table on the distribution of cases by history leaves much unanswered. We too are disappointed, and apologetic, because we were instrumental in putting them to so much trouble in acquiring results that are still inconclusive. We now wish they had run their experiment on normal primigravidas, thereby making it comparable with ours.

We also wish we had given a placebo to our controls. I would emphasize, however, that the only difference in prenatal and obstetrical care between our treated and control groups lay in the interviews of treated patients at each visit with a retired primary-school teacher, who saw to it that they took their pills every day as directed. (She was, incidentally, fully aware of our real concern about the possible dangers of stilbestrol withdrawal in patients who might be barely carrying on with the assistance of the drug, and conveyed this concern to all patients.) I, personally, never saw any of these patients and Dr. Olive Smith, being a biochemist, had nothing to do with their obstetrical management. Actually, most of the resident and visiting obstetricians were skeptical about stilbestrol and, therefore, made an effort not to be discriminating in their care.

Neither the study by Dr. Dieckmann and his associates nor ours on primigravid patients was set up for the evaluation of stilbestrol as prophylaxis against abortion. We omitted from our analyses all patients who aborted prior to viability and did not accept those who had threatened to abort at any time early in pregnancy or include such cases in our control series. We believe their figures for abortion should be based only on those patients who began taking their pills no later than the seventh week. Our figures on the prophylactic value of stilbestrol in chronic abortion are based upon patients so treated whose previous abortions had occurred before the twentieth week. For those women who repeatedly miscarry living but nonviable fetuses during the second half of pregnancy we now are certain that stilbestrol alone is not the answer. The figures just given concerning abortion, therefore, may be considered to be random.

They include essential hypertension and nephritis under the classification of toxemia. There were more such cases among the stilbestrol-treated patients than among the controls (28 vs. 17) and no information is given as to whether or not they had superimposed pre-eclampsia. If these cases are omitted, however, they found the incidence of pre-

eclampsia per se to be less in the treated primigravid and multiparous patients than in the controls. Although the number of cases is too small to make the difference significant, the fact that it was found in two of their three categories tends to confirm our results on this point.

We wish they had included in their data a more detailed accounting of the weights and lengths of infants born early. The weights are not related to gestational age and no lengths are reported. Moreover, although in Table IV prematurity by menstrual age was given for primigravid patients, no separate data are presented for prematurity by weight, the primigravid and previous abortion cases being combined to make up their group of primiparas. In this combined group no significant difference as regards the weights of the premature babies was found between treated and controls. Yet, on the basis of week of delivery there was a definitely increased incidence of premature birth among the patients who received stilbestrol. This can mean only that the infants born early to the treated mothers were big for their gestational ages and thus confirms our observation.

Our experience with the use of stilbestrol continues to be satisfactory and to confirm our previously reported clinical results. We have never claimed that it is a panacea, but after ten years of careful study and observation of patients with bad and even hopeless prognoses at the onset of pregnancy when stilbestrol was started, we are convinced that it has reduced the complications of late pregnancy and saved many babies. We trust that the many obstetricians who have been following our recommendations for the use of stilbestrol in pregnancy will realize that the paper presented this morning and the report by Dr. Ferguson fail to provide definite evidence to the contrary.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—We have not made a comprehensive study, so well designed nor so adequately controlled as to provide evidence as reliable as that presented by Dr. Davis and by the Smiths, but I would like to report a few observations which to us have seemed significant.

About the time the Smiths suggested that the ingestion of stilbestrol during pregnancy might appreciably reduce the incidence of abortion and the frequency of certain late complications of pregnancy, we had been reviewing our own experience. We had realized, as had been repeatedly reported, that while approximately 22 per cent of our patients experienced appreciable bleeding and hence might have been considered as threatening to abort, only one-third of that number actually aborted. Thus, we were looking in 1948, as indeed we are today, for means by which we might recognize the woman predisposed to abortion because of an endocrine deficiency correctable by the administration of estrogen or progesterone.

In our office since October, 1949, over 8,000 smears have been taken (as shown) from the anterior portio vaginalis of 1,851 women examined during the early weeks of pregnancy. Stained by the Papanicolaou technique, such smears have seemed to provide a practical and reliable measure of the relative adequacy or deficiency of progesterone effect. When there appears to be no deficiency of progesterone effect, practically all cells take the basophilic stain (as shown) and only an occasional cell stained by eosin indicates practically no cornification in the smears.

We have learned that patients whose smears show a relative increase in the number of cornified cells are more likely to report uterine bleeding and are more likely to experience spontaneous abortion.

For purposes of classification and in studying the apparent prognostic significance of such smears, we have learned to regard slides in which more than 30 per cent of cells show cornification (i.e., take the pink stain, as shown) as "poor smears." Having demonstrated, at least to our own satisfaction, the prognostic value of thus estimating hormone assays, we began to see if we could improve the progesterone effect and decrease the cornification evident in the smear by the administration of stilbestrol to the patient with relatively "poor smears."

We have been most interested to learn that our ability to influence the progesterone effect (as evidenced in the slide) by the patient's ingestion of stilbestrol evidently depends upon the integrity of those same means of metabolizing steroids as are characteristic of and compatible with the development of normal pregnancy. We might better express this by saying that the smear indicates an increased progesterone effect as a result of the ingestion of stilbestrol only when the early placenta can respond to the effects of such increased stilbestrol and is not merely to be expected as the result of an increased level of estrogenic substance per se.

Indeed, the cytologic response to the ingestion of stilbestrol may apparently be employed as a therapeutic test of the early placenta's ability to respond to a rising level of stilbestrol and seems, therefore, to accentuate the prognostic value of such smears. It has seemed to us, at least, that when patients with smears showing a slight to moderate increase in cornification are given stilbestrol according to the dosage recommended by the Smiths, if the number of cornified (pink-staining) cells decreases, the pregnancy will probably be maintained, whereas, if the ingestion of such "adequate" amounts of stilbestrol is followed by noticeably increased cornification, abortion appears inevitable. Actually a "missed abortion" usually becomes evident when such a smear appears after the ingestion of stilbestrol.

Our observations to date have been summarized as follows:

I.	Total number of patients with smears taken during pregnancy	1,851
	Total number of patients who aborted	123
	Over-all incidence of abortion (123 in 1851)	6.6%
II.	Incidence of abortion when smears indicated a good progesterone effect (76 of 1,620)	4.7%
	Incidence when smears indicated a poor progesterone effect (46 of 231)	20.0%
III.	Incidence of abortion when smears indicated poor progesterone effect	
	(a) with no hormone treatment given (25 in 117)	21.4%
	(b) with stilbestrol per Smith and Smith (22 in 114)	19.3%

While these data seem to suggest that such a demonstrable deficiency as exists when increased cornification appears in the smear means that abortion is more likely to occur, nevertheless 76 of 123, or 62 per cent of the spontaneous abortions, occurred in spite of a good smear. Obviously, abortion thus occurs in many instances when there is no demonstrable deficiency of progesterone effect and it has been our experience that the ingestion of stilbestrol in recommended amounts certainly does not reduce the incidence of abortion when good smears suggest no lack of progesterone effect.

In anticipation of this discussion we have recently compared the incidence of premature labor and of abruptio placentae in the group with good smears and with poor smears, and calculated the relative incidence of late pregnancy complications among the women receiving stilbestrol as compared with those not taking stilbestrol. Somewhat to our surprise we found the incidence of both premature labor and abruptio appreciably higher among the group taking stilbestrol.

In our study, groups have seemed too small to report the results in detail, but it has been reassuring to hear Dr. Davis report somewhat similar observations this morning. I have, therefore, appreciated the opportunity to record here that to date we have not observed evidence to suggest that the *postconceptional* ingestion of stilbestrol appreciably reduces the incidence of spontaneous abortion, late toxemias, premature labor, or abruption of the placenta.

DR. OLIVE W. SMITH, Brookline, Mass. (by invitation).—There are two major difficulties that Dr. George Smith and I have encountered in the controversy that has arisen over our work with stilbestrol. The first is the fact that our claims and conclusions concerning its beneficial action have been frequently misrepresented. To anyone who has carefully read our papers it will be apparent that this report by Dr. Dieckmann and his associates is no exception in this respect. We have never said that it should be given to

all women during pregnancy. Our case reports from other clinical observers were not collected at random. A record of each case was in our files at the start of the pregnancy. We do not recommend stilbestrol for the *treatment* of pregnancy complications, but on the contrary believe it is effective only when prophylactically administered. In our statistical study on primigravid women, the incidence of premature delivery was as high in treated as in control cases. We specifically stated that although the over-all fetal mortality was significantly lower in treated than in control cases, no significant decrease in the incidence of unexplained stillbirths was observed. These are the more important corrections that we feel should be made of statements that you have heard this morning concerning our clinical studies.

Our second difficulty has been the failure of other investigators, in attempting to repeat our experiments, to realize the importance of following the procedures adopted by us. Dr. George Smith has pointed out a few of the important differences between our controlled study on primigravid patients and the one reported today. I would like to say a word about the laboratory investigations. I feel called upon to do this because Dr. Dieckmann and his associates, in passing over this phase of the question, have created the impression that our many publications on this general subject and the working hypothesis derived therefrom may be disregarded since our observations on the augmentative effect of stilbestrol upon pregnanediol excretion have not been confirmed. They fail to refer to our extensive studies on the effect of stilbestrol upon the composition of the sodium pregnanediol glucuronide complex or to make clear that we were using this complex as a measure of progesterone metabolism whereas Davis and Fugo and Sommerville and his associates were measuring pregnanediol only. There is no question about the quantitative accuracy of the Venning procedure which measures this complex and it is known to recover at least two products of progesterone metabolism in addition to pregnanediol. The physiological importance of these nonpregnanediol constituents has been demonstrated. Davis himself has published confirmation of the increased output of the sodium pregnanediol glucuronide complex following stilbestrol administration. It is in the 1948 paper by Davis and Fugo. Jayle, in Paris, has amply confirmed our findings and has gained evidence, as we have, that stilbestrol causes a continued increase in the urinary output of progesterone metabolites only when the placenta is capable of being stimulated to increased secretory function.

In discussing the paper that we presented to this society four years ago, Dr. Willard Allen called attention to the classical experiments by himself and Heckel in 1939 upon rabbits, showing that estrogen prevents involution of the corpus luteum and, in this species, will actually postpone delivery through its progesterone-stimulating action. In the rodent this action is mediated by the pituitary. We extended their studies and found, among other things, that stilbestrol is more potent in this respect than the naturally occurring estrogens. And now Dr. Randall, in discussing the paper presented this morning, tells us that the administration of stilbestrol to chronic aborters in early pregnancy changes the vaginal cytology from an estrogen-stimulated to a progesterone-stimulated pattern in some cases, these being the ones in which the treatment is successful. This would seem to be an observation of fundamental importance.

As well as the progesterone-stimulating properties of stilbestrol one must also bear in mind that it is an estrogen and that the combined action of estrogen and progesterone is essential for the normal growth and development of the pregnant uterus. Four years ago Dr. Allen pointed out the effect of estrogen upon the response of the uterine muscle to progesterone, permitting relaxation so that the uterus itself can better accommodate the growing fetus. Our studies over the past 23 years have been concerned with estrogen and progesterone metabolism in women and have led to the conclusion that estrogen is essential for the normal metabolism and physiological utilization of progesterone.

Our rationale for stilbestrol therapy, therefore, is something more than a philosophy. Our laboratory experiments concerning its effect upon the excretion of progesterone metabolites have been confirmed and both our observations and those of other investigators support the concept that it is capable of exerting a beneficial effect upon the secretion and

metabolism of progesterone. The dosage is important, however. It must also be remembered that its effect is dependent upon the vascular supply and secretory capacity of the placenta. It is not a panacea but only a therapeutic agent for the rational use of which there exists a sound rationale. We feel sure that the difficulties that have arisen in this controversy would be greatly reduced if a clearer understanding of the rationale were more prevalent.

DR. BRIAN LITTLE, Boston, Mass. (by invitation).—I was very skeptical about stilbestrol in all its aspects when I was asked to add up the data on the stilbestrol-treated patients at the Boston Lying-In Hospital. The results I obtained at this time coincided very closely with those previously reported by the Smiths, and I wondered why two such eminent investigative groups should arrive at such diametrically opposite results. Then I realized that they were working with different material and that each must be considered on its own merits. Here are some of the differences:

Selection of cases has been quite different in both groups. Dr. Dieckmann has chosen all 2,000 clinic patients, including every gravidity and parity, whereas the Smiths chose a specific group, the primigravidas. These, then, are not comparable groups to start with.

In the classification or breakdown of these series, where the Chicago group has included hypertensive and nephritic patients, the Smiths have not; in fact, the figures that are reported in each paper cannot be compared for they do not represent the same entities. This is confusing.

Extraneous material has been included today in the form of abortions and congenital malformations. I think most people will agree that these must be treated, if possible, almost at the time of conception; if not then, as soon as is feasible thereafter, certainly before the seventh week for abortions and before that to have any major effect on malformations. These extra features I feel should be separated completely from this heterogeneous group because of the specific early treatment required.

Significance is a mathematical precise entity which the Smiths have used to show statistically significant figures. Today the only significance I can deduce at the moment is that stilbestrol-treated patients have a greater incidence of prematurity by dates, which has been questioned by the authors themselves who place but little faith in a woman's dates. They have inferred a little more from trends than is perhaps quite consistent with significance.

Finally, conclusions must be very carefully assessed because I think the Chicago group has misinterpreted the Smiths, as have many others, and I am sure that the conclusions of Dr. Dieckmann's group will be equally misunderstood.

Having said this, may I show you the results I obtained. These must be brief but represent eight years of diabetic patients treated at the Boston Lying-in, and five years of so-called pregnancy complications. Bad diabetics have a significantly greater fetal salvage. By "bad diabetics" are meant Classes C, D, and F of the classification proposed by Priscilla White.) This group is controlled by a similar group of patients over the same years who were not given stilbestrol. The influence of early delivery and cesarean section in these two groups is very similar, and fetal deaths in the control group occurred before either method of early treatment could reasonably have been tried. This is a controlled significant series unimpaired by early delivery.

The infants of treated mothers are significantly longer in crown-heel length. These lengths are referred to gestational age and applied to the average curves of length as reported by Yllpo and others. The untreated group showed 70 per cent normal length, and both groups showed the characteristic weight increase of infants of diabetic mothers.

In the group of habitual aborters, there were women who had had from three to ten consecutive abortions prior to treatment. The resultant fetal salvage was 73 per cent. This is significant when applied to the expected salvage, as proposed by either Eastman or Malpas. These cases, added to those reported in 1948 by Dr. Smith, represent 57 babies from 77 mothers who had been habitual aborters.

Finally, the women who had had poor pregnancy histories, which represented abortions after the twentieth week, stillborn infants, toxemia of pregnancy, hypertension or nephritis, had a fetal salvage of 68 per cent, compared with a 26 per cent salvage of their previous pregnancies. This is not a significant figure because there has been no comparable control group reported. But as I went over these cases individually, I was impressed by the results obtained in these women.

It seems, in view of these results, that stilbestrol and similar endocrine therapy should be used in diabetics and habitual aborters, at least. Recognizing that it is premature to make any startling conclusions, many of us feel that this treatment is certainly on the right path.

DR. WILLARD ALLEN, St. Louis, Mo.—The one general conclusion to be drawn from this very painstaking study of Dieckmann and co-workers must be obvious to each of us; stilbestrol is no panacea. The original work of the Smiths in which estrogen was found to be useful in preventing some of the complications occurring in the pregnant diabetic has, of course, been widely publicized. Many practicing physicians have come to believe that stilbestrol is a panacea. The drug is used prophylactically in patients who have aborted once or twice, in those who bled, and in women who have had toxemia. The results of the study by Davis and Dieckmann do not, of course, prove that stilbestrol may not be useful in some complications of pregnancy but the study does indicate that the routine use of stilbestrol does not decrease the incidence of the customary complications of pregnancy.

We have a similar study in progress. At the present time 350 patients have completed their pregnancies. Treatment was begun prior to the sixteenth week. There seems no need to give the details of the results. The material was analyzed in much the same manner as that of Dieckmann and the results were virtually identical. In short, there was no difference in size of newborn infants, duration of pregnancy, occurrence of premature labor or of toxemia in the two groups. This short series gave the same results as the much longer series. It would seem to me, therefore, that these results indicate that stilbestrol for routine use has little value.

One important question remains. How large must the sample be to give significant results? Certainly the study of Dieckmann's, Ferguson's study, and our own are as random as possible, yet in our short series some laughable irregularities occurred. The placebo series contained four sets of twins, the stilbestrol series none. Twinning occurs once in about 80 pregnancies. It is obvious, therefore, that it would require a very large series to get significant results if one were studying the effect of a particular agent in the incidence of twins. Another curious result was observed. The sex ratio was 50:50 in the placebo-treated group whereas in the stilbestrol-treated group 58 per cent of the babies were males. I mention these two observations only to indicate how dangerous it may be to draw conclusions from even a large series where the situations supposedly being affected occur rather infrequently. It seems to me that little more is to be gained by future studies of this sort. Further studies should be directed to the study of stilbestrol or other hormones in patients whose past obstetrical performance indicates a good likelihood of recurring trouble or in cases where difficulty with the particular pregnancy has already occurred.

DR. FREDERICK C. IRVING, Clearwater, Fla.—As a former Bostonian, I would be entirely lacking in civic loyalty if I had not used stilbestrol in my private practice. I have no data to present and I have very few brief conclusions which I will offer.

In the first place, I did not give it to a group of normal primigravidas so I have no conclusions so far as that is concerned. However, I feel very strongly that in the case of patients who have had in previous pregnancies hemorrhages and habitual abortions the routine administration of stilbestrol has enabled them to carry the next pregnancy to term. That is particularly true of the group of women with premature separation of the placenta before the period of viability.

My final impression is that stilbestrol does no good at all to a patient who is in the act of aborting.

DR. DAVIS (Closing).—We have followed Dr. Olive Smith's work very carefully. This experiment was designed in an attempt to learn whether diethylstilbestrol has therapeutic value. Our problem was to find out whether it is worth the time and effort and money to administer the drug to large segments of our population in an attempt to cut down on the hazards of some of these pregnancy complications.

We have not proved that it is of value. All of our data are filed on IBM cards. These are available to any of you who wish to examine them.

Concerning the length of time that the drug was taken by the patients, 15 weeks is the average time and 5 weeks is the minimum period.

We think that the number of patients studied and the methods used showed that stilbestrol has no therapeutic value in pregnancy. It is possible that that answer may not be correct, but it will take at least as many more patients just as carefully controlled to prove that stilbestrol administered prophylactically to normal or abnormal pregnant patients has any value in the prevention of the specific complications of pregnancy.

FURTHER STUDIES ON EXPERIMENTAL ENDOMETRIOSIS*

ROGER B. SCOTT, M.D., CLEVELAND, OHIO, AND RICHARD W. TE LINDE, M.D., AND LAWRENCE R. WHARTON, JR., M.D., BALTIMORE, MD.

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SAMPSON postulated the very ingenious theory of retrograde menstruation to explain the histogenesis of external endometriosis. He contended that menstrually discharged fragments of endometrium could escape from the uterus by way of the Fallopian tubes and then be implanted and grow on pelvic structures. Sampson felt that secondary growths could arise by "showering" from "incubated" primary growths. It should be stressed that Sampson nevertheless did not believe that all instances of external endometriosis could be explained on this theory alone and in later papers mentioned other possibilities, such as direct transplantation (as in cesarean section scars), metaplasia of the epithelium in amputated tubal stumps, metaplasia at the endosalpingeal-peritoneal junction, and lymphatic and venous spread. In 1940 he said: "If bits of Müllerian mucosa carried by menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten. If some of these bits are even occasionally alive, the implantation theory also is alive."

The Iwanoff-Meyer theory, championed by Novak and others, postulates that these menstrually shed fragments of endometrium are dead and incapable of implantation and that external endometriosis develops by an abnormal differentiation or metaplasia of celomic epithelium (the embryologic source of all mucous membranes of the female internal genitals). Inflammation, prolonged irritation, and hormones have been mentioned as the initiator of the celomic metaplasia. Gruenwald pointed out that in the early embryo the celomic epithelium sends cells or cell processes into the limb buds and that these cells could be the source for the rare instances of external endometriosis in the extremities. Meyer stated that if the viability of menstrually discharged endometrial particles could be definitely proved, the first question concerning the implantation, or Sampson's theory, would be answered.

Therefore, it seemed essential to determine, if possible, the status of this castoff endometrium. Since the female rhesus monkey cyclically menstruates and has a genital physiology quite similar to that of the human female this animal was used for these studies. Also there are three[3, 11, 12] or possibly more, reported instances of spontaneous endometriosis in monkeys and this present report adds another such occurrence.

*Presented at the Seventy-sixth Annual Meeting of the American Gynecological Society, Lake Placid, N. Y., June 15 to 17, 1953.

Jacobson, Markee, Harbitz, and others had shown that surgically excised endometrium was capable of autologous transplantation and growth. Two of us (R. W. Te Linde and R. B. Scott) reported in 1950 on a group of experiments, the first of which was designed to test their conclusions. In one experiment, reaffirming the aforementioned work, hysterotomies were performed on seven adult female monkeys and the surgically excised fragments of endometrium were transplanted to the anterior cul-de-sac, posterior cul-de-sac, ovary, broad ligament, rectal wall, cecal wall, and abdominal wall. One animal died of tuberculosis, but in six animals one to four transplants in each animal were found to be viable from 26 to 522 days later.

In a second experiment ten monkeys were then surgically altered to permit intra-abdominal menstruation. This was accomplished (without disturbing or cutting into intact endometrium) by cutting across the very lower portion of the cervix or across the vagina and then shifting the remaining uterus, with the blood supply preserved, to a new location within the abdominal cavity. Usually the uterus was turned through 180 degrees. Five of the ten monkeys developed endometriosis 75 to 963 days later; in four monkeys it was found in the fibrous tissue gluing bowel to cervix and in one monkey the endometriosis was extensive throughout the lower abdomen. Biopsies of the adjacent cervix revealed endocervical and squamous metaplasia, so that the endometriosis was not considered to have resulted as direct surface extension from the endometrium in the body of the uterus. These studies indicated that the menstrually shed fragments of endometrium were viable.

Three of the five monkeys which developed endometriosis were followed subsequent to the last report. Monkey No. 872 developed intestinal obstruction secondary to the extensive endometriosis and died from a perforation of the descending colon with peritonitis 3 years and 35 days after the original operative procedure. Monkey No. 889 was used for a separate study (which will be reported at a later date); this animal received 101 days of stilbestrol injections and died 3 years and 32 days after the original operative procedure. Terminally there was an exsanguinating vaginal hemorrhage and the apex of the vagina and cervical stump were completely necrotic. Monkey No. 887 is well and healthy, except for the presence of endometriosis, over 4 years after the original operative turning of the uterus.

Four of the five monkeys which did not develop endometriosis died of one or more of the following: hematocervix, hematometra, cervicointestinal fistula, peritonitis, and extensive tuberculosis. The remaining animal, Monkey No. 874, developed ureteral obstruction on the right side with hydronephrosis and hydroureter, a hematocervix, and later a cervicointestinal fistula. She survived these complications and was autopsied 4 years, 7 months, and 12 days after the original shifting of the uterus into the right side of the pelvis. The findings were most unusual and informative.

MONKEY 874.—On March 11, 1948, the lower portion of the cervix was cut across and the remaining uterus was shifted into the right posterior cul-de-sac, in order to allow subsequent menstrual discharge into this area. She rapidly lost weight, but consumed as much food as

three normal monkeys. She was tagged with the name of "Miss Bones." Two hundred eleven days after the original operation the abdomen was explored and a right hydroureter and hydronephrosis were found. She then gained weight and after another 238 days was explored and hematocervix was found. This was opened at the distal tip of the cervix and after another 137 days a cervicorectal fistula was operatively discovered and repaired. The animal continued to be apparently healthy. No endometriosis was found at any of these three exploratory procedures. Four years, 7 months, and 12 days after the original operation the animal was autopsied. The right kidney was atrophic and the right ureter dilated down to the point where the proximal cervix of the turned uterus was adherent; at this point there was marked fibrotic thickening with areas of old hemorrhage. Beyond this point of obstruction the ureter was normal in caliber and entered the bladder. There was gross evidence of endometriosis in the anterior cul-de-sac and on both upper sides of the uterus where a loop of bowel was adherent. Upon separation of the fimbriated end of the left tube from bowel a very extensive reddening and thickening was noted at this point, as though the fimbria had been an important factor in the production of this change. There was a recent corpus luteum in the right ovary (Fig. 1).

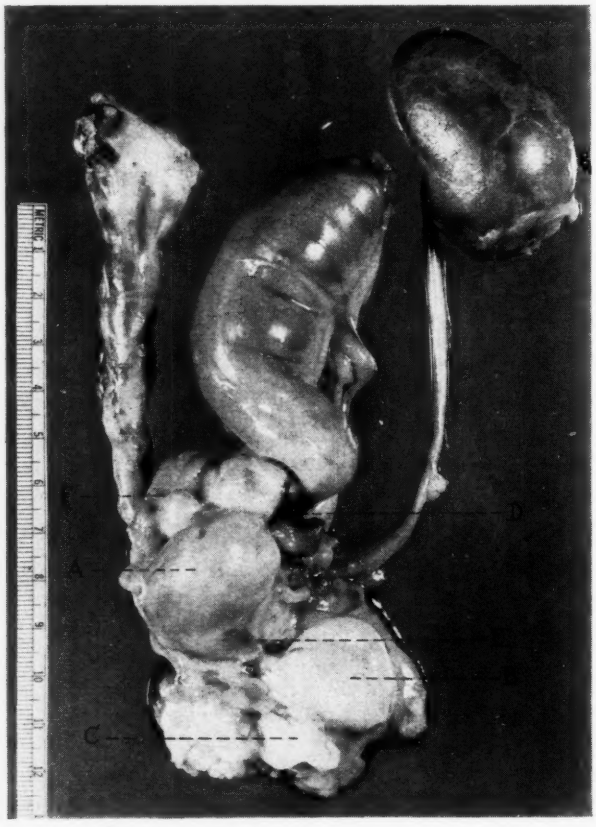

Fig. 1.—Autopsy specimen from Monkey 874, more than 4½ years after surgical alteration which shifted the uterus and permitted subsequent menstrual discharges to empty only into the right side of the pelvis. The atrophic right kidney and dilated right ureter are easily seen. *A*, uterus with proximal cervix, *B*, bladder, *C*, detached distal cervix, *D*, endometriosis involving bowel, adjacent to left tubal fimbria, *E*, endometriosis in anterior cul-de-sac, and F, corpus luteum of right ovary.

Microscopically, extensive endometriosis was found in the adherent bowel wall, anterior cul-de-sac, about the lower portion of the uterus, and surrounding the right ureter (Fig. 2). In some areas the endometrial epithelium penetrated and became continuous with the ureteral

epithelium. One paraureteral lymph node contained endometrium (Fig. 3). The endometrium within the uterus was quite normal and healthy. Sections of the right kidney showed atrophic renal tissue and in the midportion of the kidney tissue on one slide (Fig. 4) and within the capsule (Fig. 5) on two slides tiny foci of endometrial glands and stroma were found.

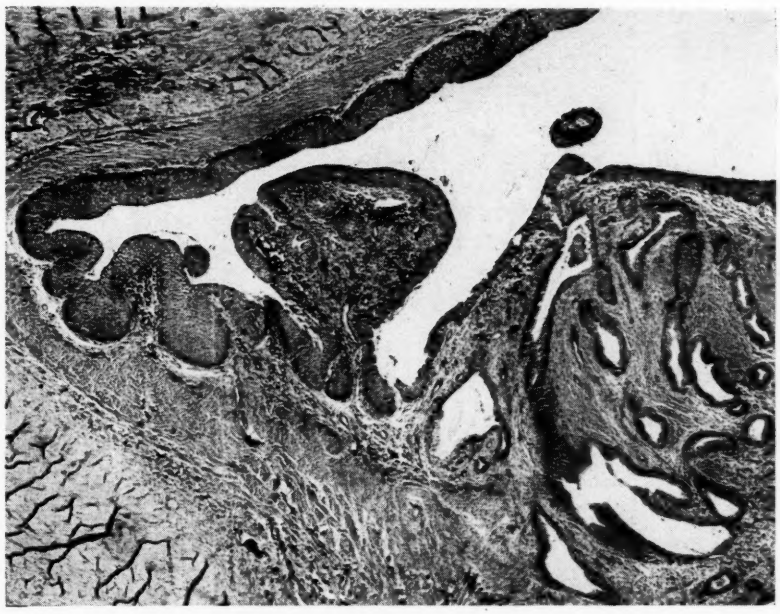

Fig. 2.—Monkey 874. Endometriosis involving the right ureter. Acini are seen containing both ureteral and endometrial epithelium.

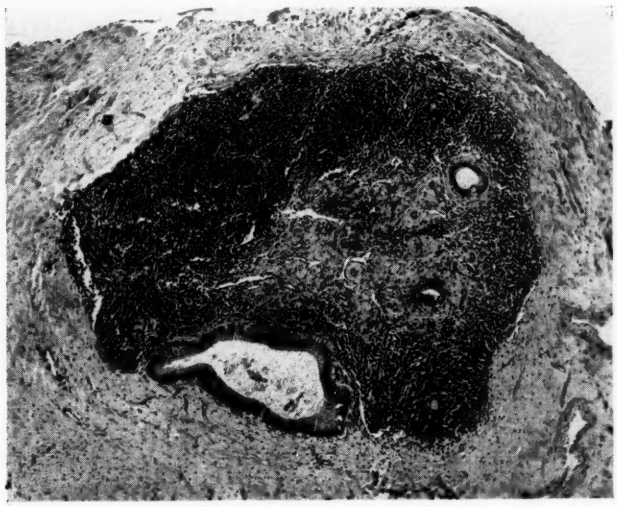

Fig. 3.—Monkey 874. Endometrial glands in a paraureteral lymph node.

Therefore, Monkey No. 874 makes the sixth of ten monkeys to develop endometriosis following an operative procedure which permitted intra-abdominal menstruation. In addition this monkey showed ureteral obstruction, secondary

to endometriosis. Endometriosis was present in a paraureteral lymph node; this could have reached the node by direct extension from nearby endometriosis or possibly through a lymphatic channel. There was no gross or microscopic

Fig. 4.

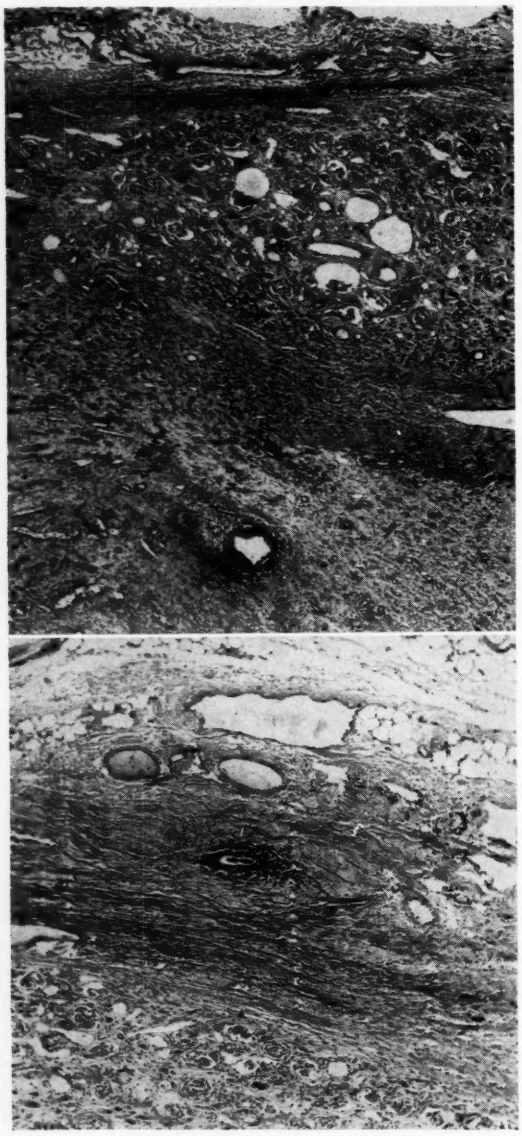

Fig. 5.

Fig. 4.—Monkey 874. Endometrial gland and stroma in medulla of the atrophic right kidney.

Fig. 5.—Monkey 874. Endometrial gland and stroma in capsule of the atrophic right kidney.

evidence of endometriosis extending up the ureter; however, sections of the atrophic right kidney showed three tiny foci of endometrial glands and stroma, one within the atrophic kidney tissue and two within the capsule. The renal

endometriosis apparently did not arise from direct extension and it seems unlikely that it "floated" up via the ureteral lumen from the point of ureteral obstruction. The location of the endometrial foci in the kidney is strongly suggestive of a retrograde lymphatic or venous spread. This same monkey had an extensive endometriosis in the bowel wall, adjacent to the fimbriated end of the left tube; the gross relationship would most logically allow for the interpretation that castoff particles of endometrium egressed via the Fallopian tube, became implanted, and grew.

One of Heim's Experiments Repeated

Heim did three experiments with monkeys and his conclusions have frequently been used to "prove" that desquamated endometrium cannot live. He opened the uterus on the first day of menstruation and scattered the intracavitary contents throughout the abdomen; 56 days later no endometrial tissue was found outside the uterus. In another experiment he did a fundectomy on the first day of menstruation, placed the hemorrhagic uterine contents in a peritoneal pouch and left the fundus open; 39 days later the fundus opening was found closed and no ectopic endometrium was identified. Viable endometrium was cut across, invalidating any conclusions as to desquamated endometrium. In addition, the period of observation was so short that any conclusions do not seem warranted. Had he waited a longer interval ectopic endometrium might have been found, because his knife cut across live, intact endometrium. In a third experiment Heim scattered human first-day menstrual discharges into a monkey's abdomen and 46 days later found no external endometriosis. Since this simulates a heterologus transplant, there is no likelihood that even freshly cut fragments of human, intact endometrium would grow in the monkey's abdomen.

The experiments seemed poorly conceived and certainly inconclusive. Therefore the following experiment was done.

MONKEY 885.—A fundectomy was performed on this monkey on April 18, 1950. The opening in the fundus was not closed. Two years, 6 months, and 5 days later autopsy studies revealed extensive endometriosis, grossly and microscopically, involving the bladder and bowel walls adherent to the top of the uterus.

Since intact endometrium was cut across in this experiment, the subsequent finding of endometriosis cannot be related to desquamated endometrium. It can be stated from the findings in this monkey that Heim was not justified in his conclusions on the basis of his short period of observation.

Blood as a Potential Agent in Producing Experimental Endometriosis

It has been suggested that blood from ruptured ovarian follicles or corpora lutea, as well as escaping blood from the ends of the Fallopian tubes at the time of menstruation, might act as an irritant to the pelvic peritoneum and as an inciter of metaplasia of this tissue to endometriosis. When fragments of live endometrium (in previous experiments by two of us) were surgically excised and transplanted to pelvic tissue and the abdominal wall of six monkeys, endometriosis was identified only at the sites of transplantation—this despite the trauma and hematogenous irritation incident to numerous exploratory

laparotomies over a time period of as long as 4 years and 5 months. When endometriosis developed after the uteri of monkeys were turned in order to allow intra-abdominal menstruation, the possibility of irritation and metaplasia of the pelvic peritoneum by the blood seemed a less likely (though not entirely excluded) explanation than transplantation and subsequent viability of desquamated endometrial tissue.

The following three questions form the background for an experimental approach to this problem:

1. Does circulating blood at the time of menstruation contain unknown constituents which are capable of altering pelvic peritoneum to produce endometriosis if placed against this peritoneum?

2. Is pelvic peritoneum essential to the production of experimental endometriosis?

3. Can the blood and serum escaping from the uterus, at the time of menstruation, separated from the endometrial elements, incite a metaplasia of pelvic peritoneum or other tissues to endometriosis?

MONKEY 901.—One c.c. of this monkey's own blood, drawn from a leg vein during menstruation on 19 occasions (cycle day one 17 times, day two once, and day four once) was injected into the lower abdominal cavity. Exploratory laparotomies 1½, 2, and 2⅛ years after the initial injection revealed no gross or microscopic evidence of endometriosis.

MONKEY 902.—From 2 to 5 c.c. (usually 5 c.c.) of blood drawn from a leg vein during 18 separate menstrual cycles (day one 12 times, day two 4 times, day three once, and day four once) were injected into the peritoneal cavity. Exploratory operations 1 year, 1 month, and 17 days, and 1 year, 5 months, and 19 days after the first injection showed no gross or microscopic endometriosis.

MONKEY 904.—One c.c. of the monkey's own blood, drawn from a leg vein on seven occasions during the first day of repeated menstrual cycles was injected into the lower abdominal cavity. The animal died of pneumonia 7 months and 9 days after the first injection and autopsy revealed no gross or microscopic endometriosis.

MONKEY 908.—From 2 to 5 c.c. (usually 5 c.c.) of blood drawn from a leg vein during 17 menstrual cycles (day one 12 times, day two 3 times, day three once, and day four once) were injected intraperitoneally. Exploratory laparotomies 1½ years, 1 year, 11 months, and 13 days, and 2 years, 3 months, and 15 days after the initial injection showed no gross or microscopic evidence of endometriosis.

In these four monkeys endometriosis did not develop in the pelvic peritoneum when venous blood, obtained during 7 to 19 episodes of menstruation was injected into the peritoneal cavity. In the period of time which elapsed (7 months and 9 days, the shortest, and 2 years, 3 months, and 15 days, the longest) venous blood obtained and injected during menstruation was not capable of causing a metaplasia of pelvic peritoneum to endometrial tissue in these four monkeys.

Consideration was also given to the experimental production of endometriosis *outside* of the peritoneum. Due appreciation was not given at the time to the significance of the second method of producing experimental endometriosis, reported in 1950 by two of us. In this experiment Monkey No. 875 was

surgically altered in order to bring one-half of the cervix, with the body of the uterus attached, out through the external abdominal wall. The cervix retracted back into the anterior abdominal wall within 2 months, and 1 year after the original operation endometrial glands and stroma were found in the scar tissue of the line of retraction. This indicated that the castoff fragments of endometrium were viable and capable of living and it should be emphasized that this occurred external to peritoneum; hence the endometriosis could not have resulted from metaplasia of celomic serosal cells. Additional monkeys were then operated upon as follows:

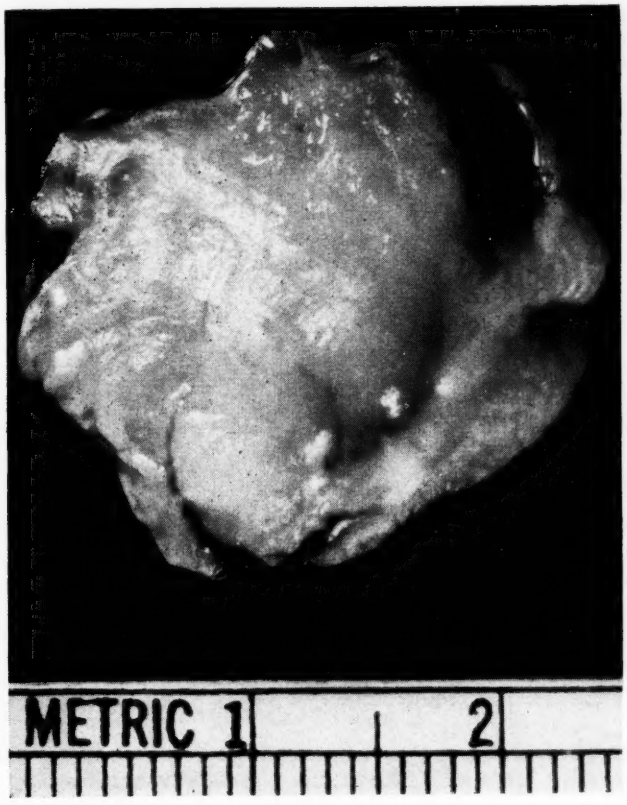

Fig. 6.—Monkey 900. Nodule of fibrous tissue, smooth muscle, and endometriosis removed from the anterior abdominal wall, more than 3 years after the cervical end of the uterus was shifted to this area.

MONKEY 884.—On Oct. 11, 1949, this animal was surgically altered. The descending branches of the uterine arteries were clamped, cut, and tied, the lower cervix cut across and the proximal cervix (continuous with the body of the uterus) was attached through the anterior abdominal wall to the skin. The skin sealed across the cervix, closing the fistula, in 5 months; 2 weeks later the covering skin was excised and the fistula remained open, discharging blood at each menstrual period. On Nov. 13, 1951, the cervix was detached beneath the fistulous tract and shifted to a new external location through the left lower rectus area. The new fistula remained open. Three hundred forty-three days after producing this fistula and a little more than 3 years after producing the first fistula, a nodule 2.5 by 2.5 cm. (Fig. 6) had developed in the abdominal wall at the location of the first fistulous tract. Microscopically this nodule showed endometrial glands and stroma with an extensive fibrous tissue and smooth-muscle response.

MONKEY 900.—This animal was found to be a normally menstruating, adult female. On March 16, 1951, the descending uterine vessels were clamped, cut, and tied, the lower cervix cut across and the proximal cervix (with adjacent body of the uterus) was shifted to the anterior abdominal wall. The peritoneum was then stripped from the proximal cervix for 15 mm. and the abdominal peritoneum attached to the remaining intact peritoneum about the uterus. The cervix was placed into the rectus muscle and the overlying fascia and skin were approximated (Fig. 7). Extensive firm scar tissue developed in the rectus muscle distal to the endocervix and 1 year and 9 days after the original procedure endometrial stroma and glands, smooth and striated muscle, and a fibrous tissue reaction were found in this area of rectus muscle (Fig. 8).

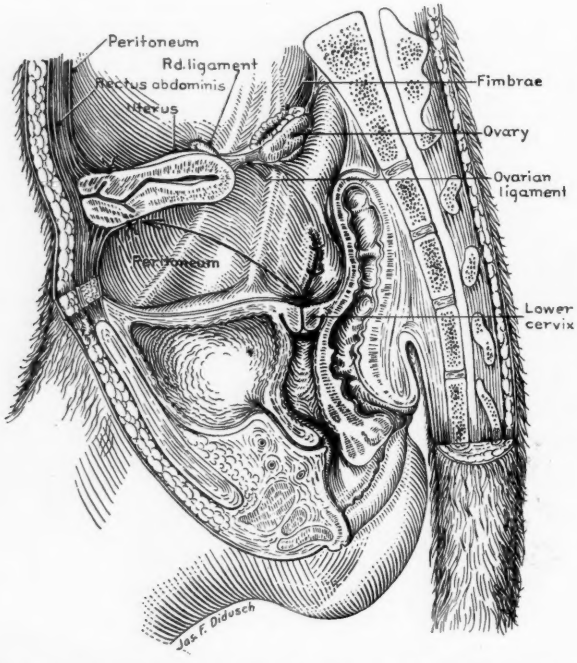

Fig. 7.—Drawing of method used to detach uterus with proximal cervix from its normal location and to shift its open cervix into the rectus muscle. Menstrually shed material could then discharge into an extraperitoneal tissue.

MONKEY 907.—This animal was an adult female which had been observed through five normal menstrual cycles. On March 2, 1951, she was surgically altered by the procedure as outlined above and shown in Fig. 7, in order to allow menstrual flow into the rectus muscle. One year and 1 month and 1 year and 7 months after the original operation endometrial stroma and glands were found in the rectus muscle; a biopsy of the adjacent cervix revealed endocervical tissue with squamous metaplasia.

In the above experiments two monkeys had abdominal wall-uterine fistulas produced and two monkeys had the proximal cervix with attached uterine body placed into the rectus muscle, so as to receive menstrual discharges. In each instance endocervix was interposed and remained between endometrium and the point of egress, as verified by the original and final biopsies. The point of discharge of the menstrual flow in each instance was external to peritoneum and in the latter two instances particular care was taken to remove all the peritoneum from the portion of the cervix which was to be buried in the abdominal wall. In from 1 to 3 years endometriosis developed in the fistulous

tracts of the anterior abdominal wall or the rectus muscles of all these animals. It therefore would appear that, in the monkey, peritoneum is not essential for the development of experimental endometriosis.

Castoff fragments of menstrually desquamated endometrium seem to be the most logical source for this endometriosis; however, unknown factors in the tissue-free menstrual discharges cannot be entirely eliminated as an etiological factor of importance. Circulating blood when injected intraperitoneally at the time of menstruation was not capable of stimulating pelvic peritoneum to the point of altering its character. Blood and serum from the uterine cavity at the time of menstruation might contain a substance capable of producing endometriosis intra- and extraperitoneally; an experimental approach to this problem has been started.

Fig. 8.—Monkey 900. Endometrial glands and stroma, smooth and striated muscle, and fibrous tissue in the rectus muscle. Specimen obtained 1 year and 9 days after the surgical alteration as shown in Fig. 7.

Can Transplanted Cervical Tissue Change to Endometrial Tissue?

Allen raised the possibility from his own work with a monkey that endocervical tissue might alter its character to produce endocervical and also endometrium-like tissue. To clarify this point cervical and endocervical tissues were removed from six monkeys by various means: total hysterectomy in monkeys 0-2 and 0-4, abdominal cervix amputation (remaining uterus anastomosed to vagina) in monkey 0-8, and incision into cervix with coning out of endocervix in monkeys 0-7, 0-10, and 0-11. The sites of transplantation and times and findings of exploration are shown in Table I.

Of the six monkeys with cervical tissue transplanted into pelvic surfaces and organs and into the abdominal wall, four showed small to moderate-sized cystic areas with surrounding thickening. Biopsies revealed endocervical (Fig. 9) and squamous epithelium (Fig. 10) lined cysts or abscess pockets, heavy subacute inflammation and some fibrous-tissue reaction. One showed only fibrous tissue

in the abdominal wall when biopsied at a later date. The sixth monkey revealed endometriosis in one ovary (Fig. 11) but it was found that in this particular animal endometrium had been cut across in obtaining endocervix and therefore this experiment had actually been a transplant of viable endometrium. Incidentally, the sixth monkey had constant vaginal spotting prior to operation and was found to have a large endocervical polyp; also the size of the uterus was three times that of a monkey of similar weight and at a similar stage in the menstrual cycle. The transition zone between the columnar and squamous epithelium of the rhesus monkey is located at a variable level; therefore, it is not unusual that both endocervical and squamous tissue were found and were transplanted. From these experiments endocervical and squamous cervical transplants studied after 182 to 669 days almost constantly remained the same type of tissue and did not change to endometrial tissue.

TABLE I. TRANSPLANTATION OF CERVICAL TISSUE

MONKEY NO.	SITES OF TRANSPLANTATION	EXPLORATION NO. DAYS LATER	FINDINGS
0-8	3 areas abdominal wall	222	Fibrous tissue
0-2	One ovary, bowel wall, apex of vagina, broad ligament, and 3 areas abdominal wall	182 and 669	Cysts lined with endocervix and squamous epithelium
0-7	Surface of uterus, one ovary, broad ligament, posterior cul-de-sac, bowel wall, and 3 areas abdominal wall	491	Cysts lined with endocervix and squamous epithelium
0-10	Anterior and posterior uterine surface, one ovary, bowel wall, and 3 areas abdominal wall	433	Cysts lined with endocervix and squamous epithelium
0-11	Anterior and posterior uterine surface, one ovary, broad ligament, lateral pelvic wall, bowel wall, and abdominal wall	203 and 459	Cysts or abscesses lined with endocervix and squamous epithelium
*0-4	Apex of vagina, one ovary, both broad ligaments, bowel wall (4), psoas muscle, and anterior abdominal wall	384	Endocervix-lined cysts. In ovary endometrial stroma and glands with heavy infection

*0-4 Incision to obtain endocervix was found to have been through endometrium.

Can Transplanted Endosalpingeal Tissue Change to Endometrial Tissue?

Sampson postulated that there could be a metaplasia of endosalpingeal tissue. He specifically felt that this was possible in the tubal stump area and at the junction of tubal mucosa and peritoneum. Endometriosis histologically may reveal ciliated and nonciliated epithelium (even peg cells), resembling tubal epithelium. Philipp and Huber felt that the interstitial portions of the Fallopian tubes, by virtue of polypoid projections of endometrial tissue, were an important source of endometriosis.

Fig. 9.—Monkey 0-2. Endocervical tissue found by biopsy from the peritoneal surface of the closed vaginal apex, 182 days after transplantation of endocervix.

Fig. 10.—Monkey 0-2. Abdominal wall transplant of cervical tissue 182 days later, showing a cyst lined by squamous epithelium and heavy inflammation.

Fig. 11.—Monkey 0-4. Endometriosis with extensive inflammation in an ovarian transplant, 384 days later. Original testing of the zone of excision for the transplant revealed it to be through endometrium, not endocervix.

Fig. 9.

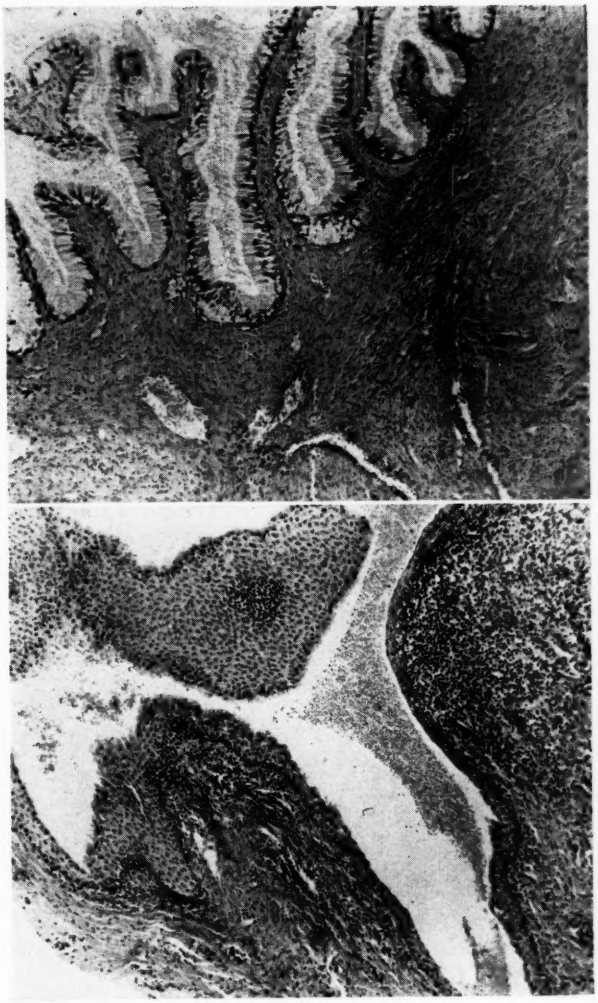

Fig. 10.

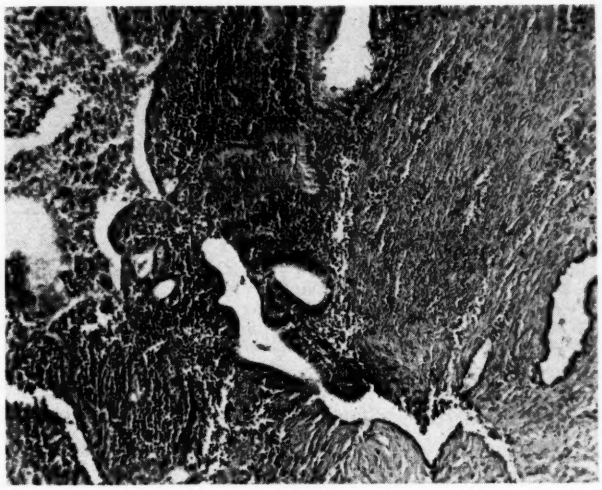

Fig. 11.

(For legends, see opposite page.)

Six monkeys (0-3, 0-5, 0-6, 0-12, and 0-18) had one or both oviducts removed at the uterine cornu. The oviducts were split transversely and fragments were transplanted to one ovary, uterine surfaces, and surface of the bowel and the abdominal wall. Some fragments were transplanted with the endosalpinx surface down and others with the serosal surface down. Biopsies at the point

Fig. 12.

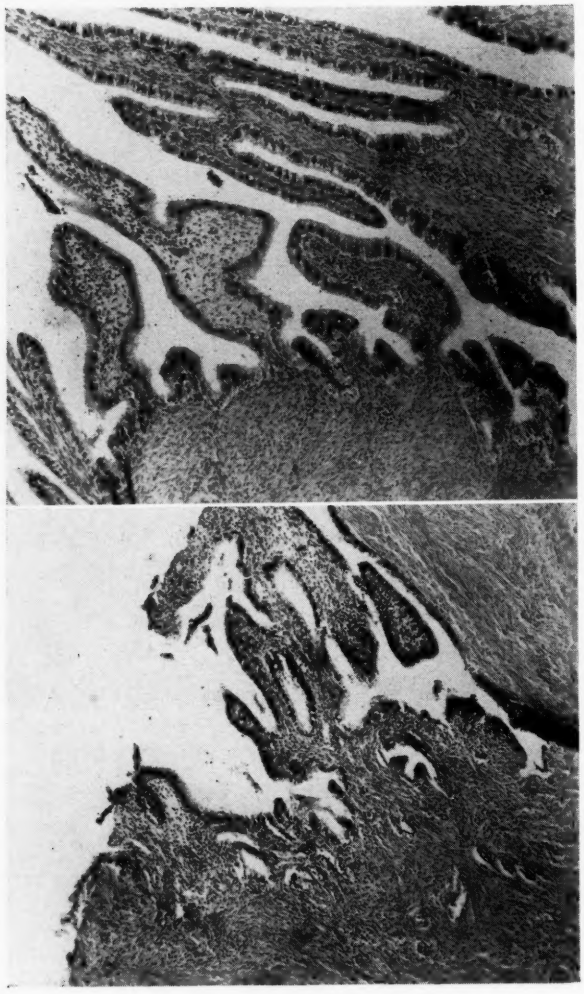

Fig. 13.

Fig. 12.—Monkey 0-6. Endosalpingeal tissue from a transplant area in the anterior cul-de-sac, 119 days after the original transplantation. No endometrial epithelium or stroma can be identified.

Fig. 13.—Monkey 0-12. Endosalpingeal transplant in the right ovary 231 days later. The epithelium is tubal in type, but areas of stroma are very suggestive of endometrial stroma.

of oviduct transection revealed no evidence of endometrial tissue in any instance. The sites of transplantation were biopsied 119 to 683 days later and on microscopic study endosalpingeal tissue alone was identified (Fig. 12), except in the case of Monkey 0-12, where an area of stroma, just beneath the epithelium, re-

sembled endometrial stroma (Fig. 13). It is realized that these studies are incomplete from a time-interval standpoint and repeated biopsies will be made over a prolonged period of time.

In summary, studies of endosalpingeal transplants over a period just under 2 years reveal no metaplasia to endometrial tissue, except in one instance where the stroma suspiciously resembled endometrial stroma.

Spontaneous Endometriosis and the Uterotubal Junction in the Rhesus Monkey

Dr. George W. Corner has turned over to our colony a new instance of spontaneous endometriosis in the rhesus monkey.

MONKEY 705.—This animal was given to Dr. Corner by Dr. Carpenter in April, 1951. Dr. Carpenter received this animal (with no known previous laboratory procedures or studies) in 1939. An abortion was recorded in March, 1940, and the ovaries were inspected following this by laparotomy. A thyroidectomy was done in 1941 and the animal delivered spontaneously at term in 1941, 1945, and 1947. Mumps virus was given during the last gestation. Exploratory laparotomies in April and June, 1951, revealed a 4 cm. cyst wall filled with brownish material and encasing the tubes, ovaries, and uterus. Biopsies of the cyst wall, omentum, and adjacent ileum revealed endometriosis.

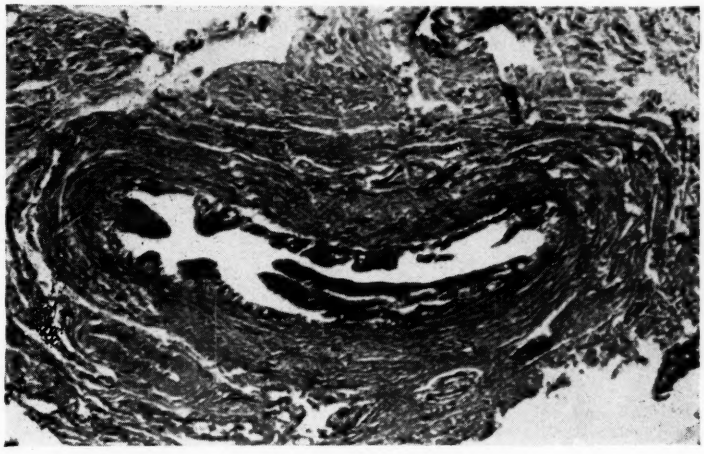

Fig. 14.—Cross section of the distal interstitial portion of a monkey's oviduct. By transparency plottings of the rest of these tubal sections the apparent mucosal folds were found to represent an artificially kinked area and not true folds.

Routine autopsy studies on these primates are rarely done and less often reported. Since this is at least the fourth instance of reported spontaneous endometriosis in the rhesus monkey[3, 11, 12] it may be hypothecated that possibly the disease is not as rare in this animal as was formerly believed.

The uterotubal junction of the monkey assumes importance in these studies when it is realized that the human female has no valve, is a cyclically menstruating animal, and at times develops endometriosis. Other cyclically menstruating primates, such as the monkey, also develop endometriosis spontaneously.

Lee found that the uterotubal junction area of the cat, dog, rabbit, rat, guinea pig, and pig were protected by a fold or valvelike membrane which prevented or impaired flow from the uterus through the Fallopian tubes. Andersen studied 25 mammals and, except in the sheep and cow, found a fold, papilla, or valvelike mechanism which impaired or prevented flow from the uterus through the Fallopian tubes.

The uterotubal junction area in the rhesus monkey has not been thoroughly studied. This animal has a bicornate uterus and the interstitial portion of the tube does not arise from the lateral, upper end but from a more superior portion. The interstitial portion is very narrow and is surrounded by three muscular coats, a middle circular coat and an inner and an outer longitudinal coat. A valve or valvelike mechanism has not been demonstrated in the rhesus monkey, although it has been assumed to be present by some authors. However, Morse and Rubin were able to do uterotubal insufflation studies in parous monkeys, indicating the absence or ineffectiveness of any such valve.

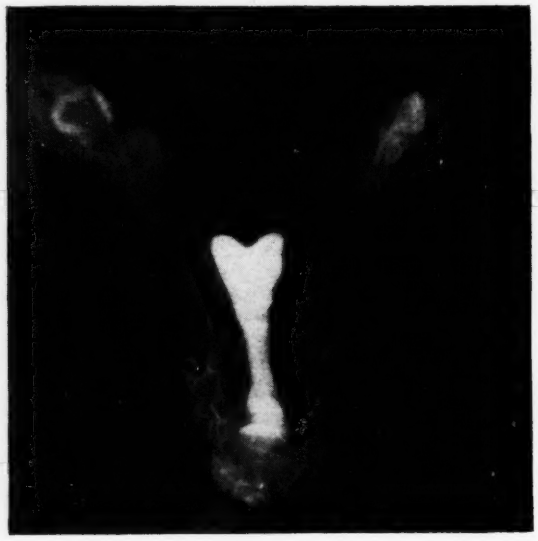

Fig. 15.—Barium and gelatin injections (via the uterus) of an immature monkey's uterus. The tubes fill with the injection medium, although the tiny proximal lumina can barely be identified.

Seven uterotubal junction (interstitial tubal) areas of four rhesus monkeys were studied by semiserial sections of fixed tissue. Only one area showed a suspicion of a valve (Fig. 14); when the semiserial sections of this tube were studied by built-up transparencies (by Dr. Corner's staff), the suspected valve was shown to be only a kinked area of the tube just outside of the uterine cornu.

At laparotomy the uteri of two monkeys were separated across the mid-cervical region and carbon dioxide was insufflated through the remaining uterus and tubes via the cervix. Gas passed out one or both tubes, on separate tests, at pressures of 30, 60, and over 300 mm. of mercury.

Injection studies of excised uteri of rhesus monkeys were then done. The tiny uterus of an immature rhesus monkey was injected with a barium and gelatin mixture under high pressure (over 200 mm. of mercury). This revealed

opaque material in the Fallopian tubes to the distal ends (Fig. 15). An adult, menstruating, female monkey had its pelvic organs removed on the seventh day of a menstrual cycle. Hysterosalpingographic studies on this uterus by an iodine oil and later by a barium and gelatin mixture under high pressure showed well-outlined tubes (Fig. 16).

From the previously mentioned studies there is no evidence to support the presence of a competent valve or valvelike mechanism at the uterotubal junction of the rhesus monkey which would prevent the flow of material from the uterus, out the Fallopian tubes, and into the peritoneal cavity. Primates, such as the human female and the female rhesus monkeys, have no valve or valvelike mechanisms at the uterotubal junction area, are cyclically menstruating animals, and have spontaneous external endometriosis. Therefore the inference of retrograde flow of fragments of endometrium as an etiological factor in external endometriosis must receive additional support.

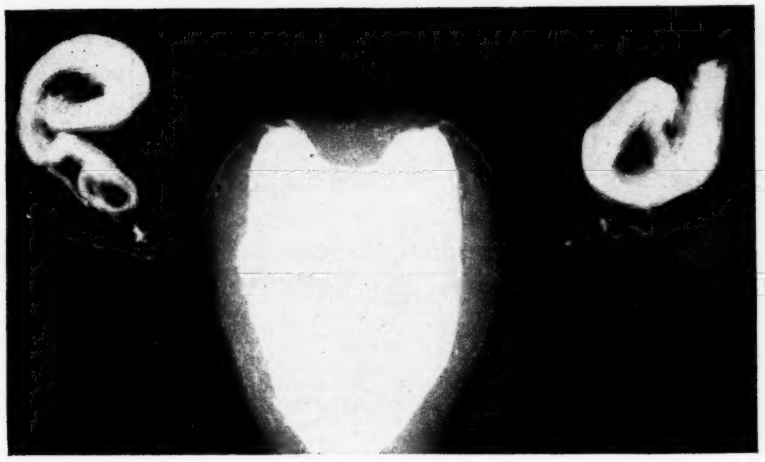

Fig. 16.—Barium and gelatin injection (via the uterus) of a mature monkey's uterus. The adequate visualization indicates the absence of any competent uterotubal valve. Note the bicornate uterus and superior location of the uterotubal junction.

Recent Studies by Other Investigators

Keettel and Stein collected second-day human menstrual discharge in a contraceptive diaphragm over a period of eight to twelve hours. Tissue cultures of this material revealed fibroblastic or epithelial growth. Javert has recently reaffirmed the clinical possibility of lymphatic and vascular spread of endometrial tissue, as suggested by others before him, including Halban and Sampson. The term "benign metastases" has been used to denote the behavior of endometrium and the similarity between the spread of endometrium and the spread of carcinoma.

Summary and Conclusions

1. Previous experiments by two of the authors are reviewed. When rhesus monkeys were surgically altered to allow intra-abdominal menstruation, endometriosis developed in five of ten rhesus monkeys.

2. A sixth monkey (out of the original ten monkeys so altered) developed extensive external endometriosis in subsequent studies. This animal showed

ureteral obstruction due to endometriosis, endometriosis in a paraureteral lymph node, extensive endometriosis involving bowel at the fimbriated end of the tube, and endometriosis in the kidney and kidney capsule.

3. A fundectomy was done in one monkey. Over two and one-half years later endometriosis was found agglutinating the uterus to bowel and bladder.

4. The repeated intraperitoneal injection of venous blood obtained at the times of menstruation did not cause a metaplasia of the pelvic peritoneum to endometrial tissue in four monkeys when observed over a period of more than two years.

5. When four monkeys were surgically altered to produce uteroabdominal wall fistulas or menstrual egress into the rectus muscles endometriosis was produced. This indicates that pelvic peritoneum is not essential to the production of endometriosis and further accents the probability that desquamated endometrial fragments are viable.

6. Transplants of endocervical and squamous cervical tissue to the pelvic organs and the abdominal wall of monkeys were studied by biopsy over approximately a two-year period of time. No metaplasia to endometrial tissue was observed.

7. Transplants of endosalpingeal tissue to the pelvic organs and the abdominal wall of monkeys were observed over approximately a two-year period of time. Biopsy studies revealed no endometriosis, except that in one instance the stromal tissue was suggestive of endometrial stroma.

8. A fourth instance of spontaneous endometriosis occurring in the rhesus monkey is reported.

9. By semiserial sections and injection studies of the uterotubal junctions of rhesus monkeys a uterotubal valve or valvelike mechanism was considered unlikely.

10. Since the human female and the female rhesus monkey have no uterotubal junction valve or valvelike mechanism, are cyclically menstruating primates, and have spontaneously occurring endometriosis, retrograde flow of desquamated endometrium is considered to be the strongest possibility in the etiology of endometriosis.

11. The reported growth of human menstrual discharges by tissue culture is noted and the clinical evidence of lymphatic and vascular spread is considered important.

12. From these experimental studies and the reports in the literature, external endometriosis in the human female is considered to be possible from: a) implantation and growth of endometrial fragments shed via the tubes at the time of menstruation, b) implantation and growth from daughter processes initiated by (a) above, and (c) lymphatic and probable vascular dissemination.

13. The metaplasia of pelvic (or celomic) peritoneum or other tissues in the pelvis is considered the least likely of all hypotheses for the histogenesis of external endometriosis.

This work was done in part under an American Cancer Society Grant recommended by the Committee on Growth of the National Research Council and in part under a grant to the Department of Gynecology of University Hospitals of Cleveland by Mr. and Mrs. Henry P. MacIntosh, III. Dr. George W. Corner and his staff of the Department of Embryology of the Carnegie Institution of Washington gave invaluable active assistance and encouragement through this and the previous work. We are indebted to Dr. Paul Hanahan of Painesville, Ohio, and Dr. Richard Nowak of Cleveland, Ohio, for their assistance in the animal operating room.

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Discussion

DR. GEORGE H. GARDNER, Chicago, Ill.—On first hearing Dr. Scott or on first reading the manuscript, it would appear that the essayists have practically proved Sampson's theory and that external endometriosis *does* arise by retrograde menstruation. However, when one deliberates on the data, he is less certain that they have presented valid evidence that the endometriosis in their monkeys actually arose from menstrually shed fragments of endometrium. The observations presented to us are factual; they did produce endometriosis. However, it is the interpretation of their findings which leads me to a divergence of opinion. For example:

First, do they have real evidence that menstruation continued in those surgically altered monkeys in which endometriosis developed. True, two animals operated upon developed hematometra and died; neither one had endometriosis. Another developed a hematocervix, which was opened, but it was more than three years later before endometriosis was found. In none of their animals that developed endometriosis (and it was chiefly around the cervix) did they mention either free blood in the abdomen or blood pigment staining of the peritoneum, both of which should be expected had these animals menstruated repeatedly into the abdomen. On the other hand, obstruction of the cervix by dense adhesions to adjacent structures was almost a constant finding, so there should have been regurgitation through the tubes, which Dr. Scott has demonstrated to be devoid of obstructing valves. Certainly there was adequate time for such pigment staining to develop, since a long, long interval had to

elapse before endometriosis developed, and at that time none of the animals had a hematometra either. What do you suppose happened to the menstrual blood? Did those animals continue to menstruate?

Second, one also wonders about the histogenesis of the endometriosis which was usually localized to the area around the adherent intra-abdominal cervix. It would have been more convincing had they serially sectioned these cervices since—Dr. Scott to the contrary—biopsies per se are inadequate to exclude the possibility of *downgrowth of endometrium* from the corpus, through the cervix, to the peritoneum.

Third, their Monkey No. 874 is extremely interesting, and for many reasons. When surgically altered, the cervix was shifted into the right posterior cul-de-sac. Within 7 months a right hydroureter and hydronephrosis were found, but no endometriosis—it was too soon. (Incidentally, in 1950 it was reported that this ureter had probably been obstructed through faulty technique at the time of the surgical alteration.) In another 8 months a third laparotomy was required to open a hematocervix, and within 4½ months, she was operated upon for the fourth time, to repair a cervicorectal fistula. Still no endometriosis was discovered. However, when sacrificed more than 4½ years after the original surgery and 3 years after the fourth laparotomy, there was extensive endometriosis on peritoneal surfaces, also around the right ureter at the site of obstruction, in an adjacent lymph gland, and in the right kidney.

My point is this: Perhaps all of these experiments could have been more accurately controlled to exclude metaplasia as a cause of the endometriosis, especially since (a) rhesus monkeys are susceptible animals and develop endometriosis spontaneously, and (6) no one seems to understand why it takes so long—many months or even years—for experimental endometriosis to develop. Certainly one is justified in assuming that repeated laparotomies cause peritoneal irritation, which may produce adhesion and which conceivably could result in metaplastic transformation of peritoneal tissues. Such a possibility might have been excluded had they used paired controls, which were subjected to an equal number of laparotomies with the same degree of trauma and the same biopsies, except that in the controls the uterus and adnexa remained in situ.

Further, it is hoped that someone will produce cervical atresia by vaginal operations on a series of adult monkeys but not perform laparotomies on them for at least three or four years thereafter. Certainly, if the authors' thesis is correct, this simple experiment should cause tubal regurgitation and produce pelvic endometriosis.

DR. EDWARD D. ALLEN, Chicago, Ill.—In discussion of the previous report we asked a question concerning the probability of metaplasia of cervical epithelium; it seems that the authors have answered this in a very convincing way.

May we ask another question centering about the cervix? In our previous series, multiple surgical procedures were carried out. In our present one, almost completed (unreported), a minimal amount of surgical trauma has been produced. In both series we have implanted the cervix into the anterior abdominal wall, as have the authors. In the first series, experimental endometriosis was found inside the peritoneal cavity in 66 per cent of the cases. In neither series have we found extraperitoneal lesions about the external os of the cervix. The authors found 100 per cent. Could this difference be due to the additional trauma of the cervical amputation? We have known for years that endometriosis appears in postoperative scars in women.

The beautiful example of endometriosis found in their Monkey No. 874 apparently, did not appear until some time after 586 days and then most conspicuously in those areas where major multiple surgical traumas had occurred. This was likewise true in our first series.

Time seems to be one of the important elements in the production of these ectopic lesions. This experimental method seems to have great promise.

DR. EMIL NOVAK, Baltimore, Md.—The older Fellows will recall the thrill everyone got in 1921 when Sampson presented his first paper before this Society. Though we hear

many excellent papers, there are some that just hit one between the eyes, so that one knows at once that they are epoch making, and that was certainly true of Sampson's paper. Many of you older men will also remember that for a number of years following Dr. Sampson's presentation there was an annual discussion of this subject before this Society, that the divergent views as to its etiology gradually began to come together, so that Dr. Sampson in his latter years made no claim whatsoever as to the universal applicability of his theory of menstrual regurgitation. The advocates of the celomic theory also began to meet Sampson halfway and to recognize that endometriosis can at times come from implantation of endometrial tissue. An endometrial cyst, for example, may perforate and deposit the seed in the uterosacral ligaments or elsewhere. I shall not comment at length on the paper presented today, because I had the opportunity to discuss the first paper by the present authors presented 2 years ago, and the comments Dr. Gardner has made this morning are somewhat similar to those I made at the time of the original presentation.

I believe the present study goes farther than any previous one in establishing the implantability of endometrium which has been cast off at menstruation. There are still a few flaws in the study, as Dr. Gardner has pointed out, and it must be borne in mind that the study touches on just a small angle of the question of the etiology of endometriosis, which is almost surely not always the same. We have known for many years that endometrium can be implanted on the peritoneum. Shortly after Sampson's first paper, his co-worker, Jacobson, implanted endometrium on the peritoneum, but the question then arose as to whether we could apply this to an explanation of Sampson's regurgitation theory. There was a big difference between the healthy endometrium Jacobson implanted and the degenerated endometrium cast off at the time of menstruation. The paper today bears on that particular point, whether castoff endometrium can be implanted. Even conceding that this point has been established, it still represents only one small angle of the whole question of the etiology of endometriosis.

I recently talked to a distinguished embryologist who said there is no site of endometriosis which cannot be explained by the celomic theory. One can certainly not say that that is the explanation of all cases, though it must be invoked in some. It is probable that the lymphatic theory of dissemination, which has not been taken too seriously, has to be considered in certain locations, as would appear from Javert's recent paper. We have all found endometriosis in the lymph glands occasionally, but by more intensive search Javert found many instances of endometriosis of the lymph glands. Whether or not this has any clinical significance or any bearing on the general question of the etiology of endometriosis is not very clear.

DR. KARL H. MARTZLOFF, Portland, Ore.—What I want to ask is: Did the extrauterine pelvic endometrial implants in these animals show any evidence of menstrual activity? If there was no evidence of menstruation, as Dr. Gardner has indicated, in the absence of blood pigment, then did the gland architecture in these extrauterine implants correspond in menstrual-cycle pattern to the endometrium that was present simultaneously in the uterine cavity? Also, did these extrauterine endometria show evidence of hormonal stimulation, as is often found in human extrauterine endometrium?

DR. ERLE HENRIKSEN, Los Angeles, Calif.—I would like to get on the human side of this problem. As Drs. Scott, Te Linde, and Wharton continue adding experimental support to the implantation theory, it seems proper at this time briefly to report a series of three cases of endometriosis. I do this not with the premeditated intent of adding more confusion in the search for the true theory or theories of etiology (Table I). The report consists of the singularly similar pattern of endometriosis occurring in identical triplets. It is noted that, despite the early marriage and subsequent pregnancies of Sister No. 3, the onset of symptoms, the presenting pathology and the type of treatment are almost identical. In favor of early marriage are the two babies of Sister No. 3, as against the price of delayed opportunities for pregnancy by marriage in the other two sisters.

It is difficult to account for the similarity of the disease pattern in these cases by any of the theories now in vogue. For need of a good explanation, it is probably necessary to

consider the influence of heredity. On the advice of Dr. Scott we carefully examined the uterotubal junctions of Sisters No. 1 and No. 3, and we could demonstrate no abnormalities.

TABLE 1.

AGE YEARS	SISTER NO. 1	SISTER NO. 2	SISTER NO. 3
14	Menarche	Menarche	Menarche
16	Dysmenorrhea	Dysmenorrhea	Dysmenorrhea
18	Nurse's training	Nurse's training	School
20	------	------	Married
21	------	------	Normal child
22	------	------	Normal child
23	D & C	D & C	------
24	Surgery, conservative	D & C	------
25	Married	Surgery, conservative	D & C, D & C
26	------	------	D & C, D & C
27	Surgery, complete	------	------
28	------	Married	Surgery, complete
29	------	Surgery, complete	------

DR. SCOTT (Closing).—Dr. Gardner asked about evidence of continued menstruation in the surgically altered monkeys. In some animals the distal portion of the cervix was transected before the uterus was shifted and in others the vagina was cut across. In many of these animals subsequent vaginal aspirations would periodically reveal blood. I could not conceive of the actual source of this blood until autopsies were done on two of these animals. A fistulous communication was found between the vagina and the endometriosis about the tip of the shifted cervix. Some of the biopsies of the experimental endometriosis revealed pigment-laden macrophages as evidence of bleeding from these areas of ectopic endometrium. As further evidence of continuing menstrual function, many corpora lutea were found at the time of exploration and at autopsy secretory endometrium was found on several occasions. Basal temperature readings were not taken. Endometrial biopsies were not done since these are practically impossible to obtain via the Z-shaped cervical canal. A hysterotomy for endometrial biopsy would have been contrary to the basic principles of this study, since intact endometrium would have been cut across. This would ruin the animal for further studies and at the current cost of monkeys conservation was quite necessary.

Dr. Gardner asked why we did not see evidence of regurgitation through the tubes. It was only in animal No. 874 that there had apparently been regurgitation through the tube. Morse and Rubin, as well as the present workers, were successful in performing Rubin's tests on monkeys, although the pressure necessary was usually quite excessive. In the injection studies the amount of pressure necessary to fill the tubes was quite high. In addition, the interstitial portion of the tube has a very tiny lumen, is curved, and is surrounded by three bundles of muscle fibers. I doubt that the back pressure developing in one of these blocked uteri at the time of an ordinary menstrual period would, but rarely, be sufficient to force the blood out through the tubes.

In our previous studies numerous biopsies and the autopsy studies did not reveal any continuity between the normal endometrium and the experimentally produced external endometriosis.

Surgical irritation could be the factor responsible for this endometriosis, but this is quite unlikely. In our experiments with transplantation of surgically excised endometrium, endometrial glands and stroma were found (over more than 3 years' observation) only in the immediate area of the transplants.

Dr. Allen wondered if the transection of the cervix could be a factor. The transplants of cervical tissue in the six monkeys did not change to endometrial tissue. In our previous experiments monkey No. 847 developed external endometriosis following shifting of the uterus; in this instance the incision was across vagina but not across cervix. These facts suggest that an incision across cervix was not of etiological significance in our experiments.

All of us know Dr. Novak's long and continuing interest in this subject and his many contributions which have added to our understanding of this disease. I, too, believe that there is no one explanation for the histogenesis of external endometriosis and, as time goes on, more individuals are coming to this belief.

Dr. Martzloff asked if there was any evidence of hormonal influences on the abdominal wall transplants. No correlation could be made between the appearance of the endometrium in the experimentally produced endometriosis and the normally located endometrium. We did not take endometrial biopsies and since there was no visible menstrual flow, we could not determine the relationship of abdominal wall biopsy to the time in the menstrual cycle.

These studies have seemed to clarify some of our clinical findings. Keettel and Stein's successful growth of second-day, human menstrual discharges in tissue culture and Javert's re-emphasis of lymph node endometriosis are in line with our findings and concepts. A recent patient of Dr. Robert Faulkner's showed endometriosis in the fossa remaining after a Bartholin gland excision (which had stayed open and raw for several months after the excision). Kistner and Hertig reported endometriosis in a fistulous episiotomy tract many months after the original breakdown and slow healing of the episiotomy. These raw areas in the two patients, exposed to several episodes of menstrually shed endometrial fragments, could offer a fertile nidus for implantation.

To my knowledge, external endometriosis has not been found in the male or in pseudo-hermaphrodites, who do not menstruate. Were celomic metaplasia an important factor, the genital jigsaws should frequently have endometriosis.

The late Dr. John Fallon considered endometriosis a quasi-cancer, occupying the gray zone between frankly benign and frankly malignant. Javert's term "benign, metastasizing tumor" for this disease seems quite appropriate. With these concepts in mind, umbilical and distant endometriosis could be explained in the same manner as umbilical and distant metastases from an intra-abdominal cancer.

An extreme postulation might be made. If serial section of all pelvic tissue were feasible, might not all 40-year-old women with patent tubes and normal menstrual cycles, regardless of parity, reveal some endometriosis?

Much important work still remains to be done, not only on the histogenesis of external endometriosis, but on the trigger mechanism and unknown factors which will allow stagnation of the process for years in one instance and phenomenally rapid growth in another instance.

OBSERVATIONS ON THE PATHOGENESIS OF PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA*

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PLACENTAL abruption was produced experimentally and at will by Howard and Goodson,[1] in this laboratory in the dog, by ligation of the vena cava below the level of the renal veins and ligation of the left ovarian vein. Success with the animals immediately raised the question whether or not this could be duplicated in the human being.

Placental abruption, or ablation, or premature separation of the normally implanted placenta can be so inimical to fetal, and even to maternal, life that one does not lightly contemplate its deliberate production. On the other hand, it is generally conceded that the etiology is unknown. Therefore, any light which could be shed upon the situation might justify a calculated risk. After much thought it was decided to look for a multigravida with many living children and in need of a cesarean hysterectomy. At the time of a proposed cesarean hysterectomy, with the pregnant uterus resting upon the anterior abdominal wall, we could compress the inferior vena cava manually, extract the child, and remove the uterus with a minimum of delay. Thus the situation would be under control at all times. Since Howard and Goodson produced abruption in one dog by venous obstruction of only 5 minutes' duration, we elected this span of time. It was argued that total venous obstruction would not begin to produce fetal hypoxia at once. Furthermore, we estimated that fetal anoxia would not persist more than 3½ minutes if a 5 minute inferior caval compression were performed.

In the dogs, both the inferior vena cava and the left ovarian vein were ligated. We believed occlusion of the left ovarian vein was unnecessary and did not touch it in the human being. The relatively minor anastomotic circulation by way of the left ovarian and renal veins was not deemed capable of carrying sufficient blood on short notice to affect the result. Moreover, there was precedent to guide us, since we have repeatedly observed and recorded arterial pressure drop and femoral venous pressure rise in the human being with the supine hypotensive syndrome. This syndrome is a naturally occurring phenomenon, shown by Howard, Goodson, and Mengert[2] to be due to compression of the inferior vena cava by the near-term pregnant uterus. Probably compression of the ovarian veins does not enter into production of this syndrome.

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The First Patient.—

Early in April, 1953, a grande multigravida at term was seen for the first time and admitted with a story of ruptured membranes and painful uterine contractions during the preceding 24 hours. The cervix was partially effaced and 4 to 5 cm. dilated. Recognizing a probable cephalopelvic disproportion, principally because of the large size of the child, we decided to perform cesarean hysterectomy.

The abdominal incision was made sufficiently long to allow delivery of the pregnant uterus. The bladder flap was dissected downward in anticipation of a low segment incision. It was noted that the round ligaments diverged, indicating the placental site to be on the anterior wall. The uterus looked quite normal, and its coloring was unaltered. The abdominal aorta was located by palpation, and from this landmark the inferior vena cava was located. The vein could be felt as a collapsible and refillable structure, about the size of a man's thumb. A point below the entry of the renal veins was selected, and the vena cava completely occluded by digital compression with the fingers of one hand, and by pressure of a sponge on an ovum forceps held in the other hand. The aorta was not compressed. The supine hypotensive syndrome promptly began to appear (Fig. 1). The systolic blood pressure dropped from 140 mm. of mercury to 68 in about 60 seconds.

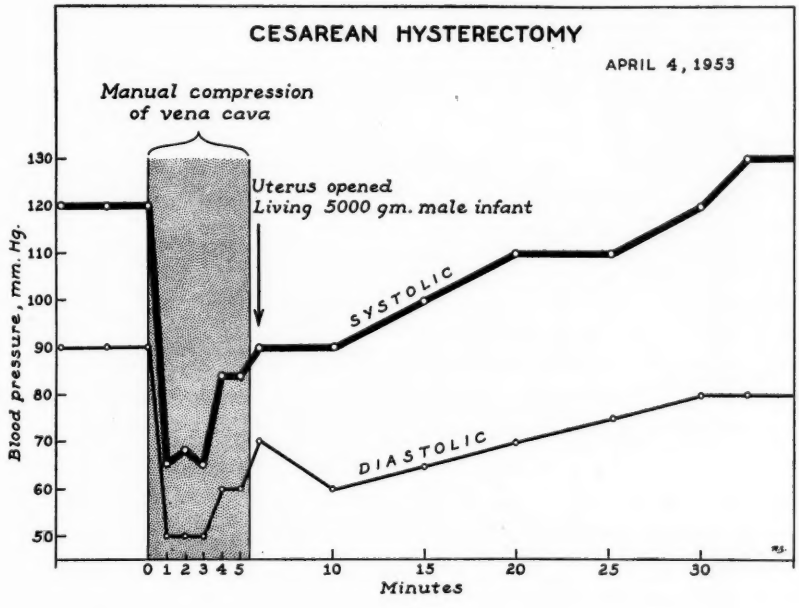

Fig. 1.

The entire uterus then began to exhibit vascular congestion, especially in a circular area as big as a man's open hand on the anterior wall. After about 3 minutes, this area became dark red in color and elevated above the surrounding uterine wall. In the center of the placental site the elevation was estimated to be 1 cm. At the end of five minutes and 30 seconds, caval compression was released and a male child extracted through a transverse lower uterine segment incision. He was resuscitated without difficulty, and weighed 5,000 grams.

Immediately following extraction of the child, the placenta presented and large amounts of dark blood, estimated to be several hundred cubic centimeters, flowed from the uterus behind the placenta. This blood was quite distinct from, and much darker in color than, the venous blood flowing from the cut edges of the uterus. A hand was inserted into the uterus, and the placenta found to be *almost completely separated except for a small area at*

its upper edge. Total hysterectomy was performed and the uterus opened. There was old dark blood covering about one-half of the placental site. Corresponding areas of dark blood were seen on the maternal surface of the placenta.

With release of caval compression, the patient's blood pressure gradually rose to normal.

Altogether, this was a convincing demonstration. Not only was extravasation of blood produced at the placental area, but also, there was almost a total separation of the placenta. Obviously, it was impossible to continue the experiment to the point where clinical symptoms and signs other than acute hypotension might have ensued.

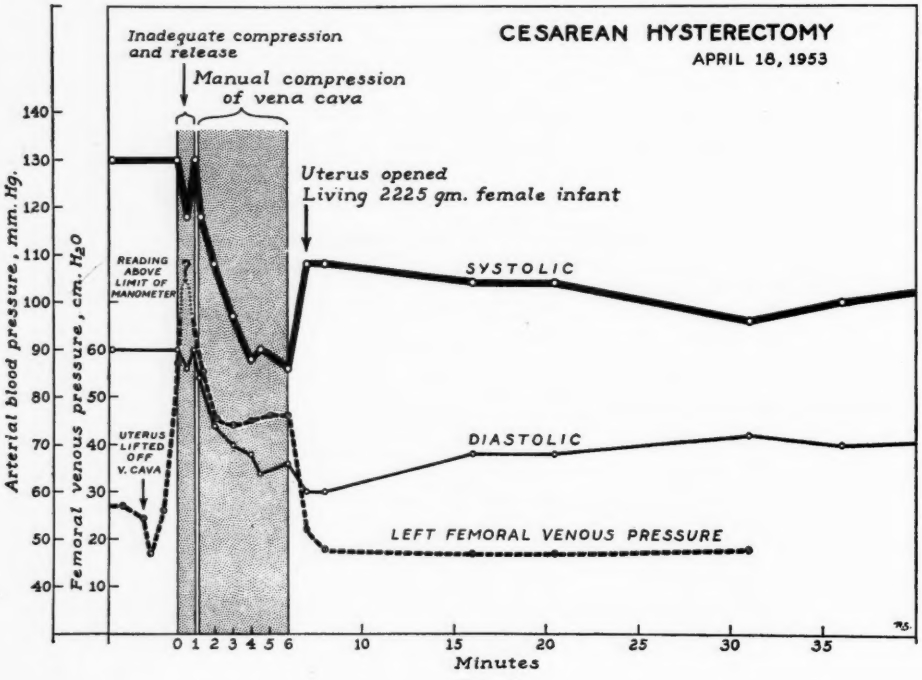

Fig. 2.

The Second Patient.—

Prior to operation, a polyethylene catheter was introduced into the left femoral vein. The abdomen was opened with an incision extending above the umbilicus. The entire uterus was placed unopened on the abdomen and the bladder flap dissected downward. The round ligaments were divergent from below upward, and there was a circumscribed tracery of veins, indicating that the placenta was on the anterior and superior surface of the right side of the uterus. The aorta was identified above the bifurcation of the common iliac arteries. The inferior vena cava was located and compressed for about one minute, but we were not satisfied that the compression was adequate. Therefore, the pressure was released, anatomic reorientation achieved, and the inferior vena cava again compressed. This time the typical hypotensive syndrome developed (Fig. 2). In about two minutes the uterus exhibited a dusky hue and the placental site began to be injected. At the end of five measured minutes the uterus was opened transversely in the lower segment and a 2,225 gram female child extracted and resuscitated without trouble.

Immediately following the birth of the baby, a huge clot of dark blood enclosed by amnion appeared in the opening. The placenta was palpated, and, as previously noted, was attached to the anterior wall. An area of separation shaped like a keyhole had occurred

in the center of the placental area with the channel of the keyhole leading to the lower segment incision. It was estimated that between one-fourth and one-half of the placenta was separated. The amnion-enclosed clot was opened. In order clearly to demonstrate the central separation of the placenta, the uterus was opened anteriorly before removal. The darkened, separated area was readily seen. Routine total hysterectomy was performed.

Although this demonstration was not as dramatic as the previous one, it was, nevertheless, convincing. The vascular congestion of the uterus, the immediate presentation of dark, retroplacental blood accidentally encapsulated in amnion, palpation of the separated area, and the demonstration of separation after incision of the uterine wall while the organ remained in situ leave little doubt of the production of placental abruption. One may speculate as to why only one-fourth to one-half of the placental surface abrupted, whereas in the first patient there was almost total separation. An obvious, although not necessarily a correct, answer is suggested by the discrepancy in fetal size and duration of pregnancy. Another possibility is that the cava of the second patient was not compressed as adequately as was that of the first patient.

Histologically, relatively little was seen. Since all the antecedent events were acute, extensive tissue changes would be difficult to reconcile with the precipitating force and its timing. In addition to the customary histologic features of pregnancy, sections of the human uteroplacental junction showed varying degrees of recent hemorrhage into the superficial layers of the decidua. Early clot formation was seen in a few areas, but no tissue disruption or fibroblastic proliferation. Since there would in neither case have been time for even the earliest changes of organization, it was hardly surprising that evidences of fibrin network deposition were insignificant. No tendency to hemorrhagic disruption of the myometrium was observed beyond a few focal hemorrhages in the muscle just adjacent to the decidua basalis in one slide.

An acute placental separation produced experimentally in a normal patient or animal would not be expected to present any pathognomonic or specific histologic changes, and these sections bear out such a supposition. If time were allowed to elapse between the artificially produced obstructive episode and ultimate removal of the uterus and placenta, extensive and well-defined lesions might be encountered. We propose to make such studies in the immediate future in at least two species of experimental animals.

Comment

It would be folly to claim that obstruction of venous outflow from the pregnant uterus is the only cause of placental abruption. On the other hand, by this method alone, we produced acute placental abruption in two pregnant women at term, and Howard and Goodson,[1] working in this laboratory, produced it in 5 pregnant dogs in the second semester of gestation. Barcroft, Herkel and Hill,[3] experimenting on the rate of blood flow in the uterus of the pregnant rabbit, were "much impressed with a tendency of even moderate pressure on the uterine vein to produce intra-uterine hemorrhage," but did nothing to follow this up.

Much earlier, in 1918, Morse[4] produced abruption in one horn of the uterus of the pregnant rabbit by ligation of the ovarian, the mesometric, and the uterovaginal veins leading away from the horn. He stated, "What blocks the veins in human pregnancy occasionally is still a matter of speculation," and then hinted it might be rotation or forward displacement of the uterus resulting from a lax abdominal wall. Morse's work was ignored, and has been forgotten in the ensuing years. Probably this was because of the difficulty of relating it to the human being.

Today, we know that about 11 per cent of pregnant women near term exhibit the hypotensive shock syndrome if they lie on their backs for even a few minutes. Also, we know that this syndrome is caused by compression of the inferior vena cava by the flaccid pregnant uterus. Possibly, many other gravidas near term suffer varying and unrecognized degrees of partial compression of the inferior vena cava. Certainly we know that a woman in late pregnancy seldom lies on her back by choice. Also, we know that a sufficient amount of compression of the inferior vena cava exists in every woman in late pregnancy lying in the supine posture to raise the femoral venous pressure two or three times above normal. This elevation of femoral venous pressure immediately disappears if: (a) the woman stands erect, (b) she turns to either side, (c) the pregnant uterus is manually lifted anteriorly during cesarean section.

Thus the relationship is clear and we now have a simple and direct etiological concept of one type of placental abruption. Presumably, other etiological factors remain to be discovered in the future.

A flood of clinical implications comes to mind, and many of the questions engendered have been asked of us, either by ourselves or by others. The questions cannot be answered at this time. On the other hand, we cannot refrain from speculating regarding a certain obstetric incident familiar to all of us.

This concerns the recumbent patient, successfully delivered of a living child, in whom the detached placenta follows immediately and presents at the vulva, attended by more than the usual quantity of blood, somewhat darker than normal. We believe this patient may have suffered placental abruption in the closing minutes of labor. We also are inclined to believe the abruption may have resulted from an embarrassed venous outflow from the uterus.

Summary

Placental abruption was produced in each of two women at or near term, during the course of cesarean hysterectomy, by the simple expedient of digital compression for 5 minutes of the vena cava below the level of the renal veins. Probably this is the first time placental abruption has ever been deliberately produced in the human being. Both mothers and children survived and are prospering.

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Discussion

DR. DUNCAN E. REID, Boston, Mass.—Until the present time, the explanations offered for the etiology of premature separation of the placenta have been based mainly upon the findings in studies of the uterine and placental pathology of this complication of pregnancy. Little attention has been given to the deviation in normal uterine physiology which must precede these morbid changes, in the production of this syndrome. It is this particular aspect of the problem which Dr. Mengert and his associates have proposed to study, both by animal experimentation and clinical investigation.

Interference in the afferent flow of blood to the intervillous space is commonly believed a prerequisite to the development of premature separation of the placenta. How this is brought about has received various theoretical interpretations. The decidua serves to support the placenta, particularly the decidual blood vessels which enter and leave the intervillous space. It is conceded that, with growth, there is also some degree of degeneration and necrosis of the decidua during normal pregnancy, more especially in the last trimester. Should the decidual changes become accentuated, the blood vessels within the placental site lose their normal support, collapse, and rupture. The result is local bleeding and placental separation. The sequence of events is comparable and indeed may be quite similar to the endocrine withdrawal effect on the endometrium and the spiral vessels which precede and accompany menstrual bleeding. Presumably in pregnancy the changes in the decidua may become aggravated by alterations in the normal function of the blood vessels of the placental site. The increased frequency of premature separation associated with pregnancy toxemia is believed to be the result of spiral vessel involvement, a local manifestation of a diffuse vasospasm.

Disruption of the fetal blood flow has its advocates as a cause of premature separation. Trauma to the blood vessels over the fetal surface or within the substance of the placenta presumably may lead to infarction and secondary involvement of the intervillous space with eventual premature separation.

The majority of patients, however, with premature separation of the placenta are free of toxemia. A small number of patients in this group may have placental anomalies, particularly circumvallate placenta, but in most instances there is no apparent cause to account for the placental detachment. It seems plausible, therefore, that, in certain instances, factors other than deciduous necrosis and intrinsic dysfunction of the blood vessels of the placental site or the fetal vessels are responsible for the complication.

Dr. Mengert and his group have postulated that interference with the efferent or venous flow of the maternal blood from the uterus, presumably with resultant acute venous engorgement of the intervillous space, is an etiological factor in abruptio placentae. These workers contend that compression of the inferior vena cava will cause the latter to occur. They also hold the opinion that, with the patient in the supine position, the pressure of the term uterus on the inferior vena cava might on occasion raise the intrauterine venous pressure sufficiently to cause placental detachment. The evidence for these views is derived from at least three sources: The first is the experimental production by Dr. Mengert and his associates of premature separation of the placenta in the dog by a low-level occlusion of the inferior vena cava. Second, is the apparent placental separation following digital compression of the inferior vena cava at the time of cesarean section herein reported. The third is the evidence drawn by Dr. Mengert from the clinical observation that the symptoms af dizziness and faintness, rather frequent complaints of patients when placed in the supine position in the last trimester of pregnancy, can be associated with transient and marked hypotension. The stimulation of the regional ganglia of the autonomic nervous system by the enlarged uterus is the reason generally offered to account for these symptoms and the fall in blood pressure. In Dr. Mengert's patients, rather than a bradycardia, however, the hypotension was associated with a tachycardia. This is suggestive that the hypotension is the result of a shocklike state rather than being of neurogenic origin. This would favor Dr. Mengert's thesis that, under the circumstances, the weight of the term uterus may compress the inferior vena cava sufficiently to interfere

with normal return of blood to the heart. The status of the cardiac output would be crucial information in the differentiation between the two possible causes of the hypotension. A reduction of cardiac output would occur in the case of shock while cardiac output is said not to change in vagal syncope. Newer techniques utilizing the dye method while not simple are safe.

The basic consideration in the evaluation of this experimental method to the clinical entity of premature separation of the placenta is the redistribution of blood following compression of the inferior vena cava. The infrequent occurrence of this condition attests to the fact that the blood in normal pregnancy is reallocated following changes in posture without any detectable effect on the uterine circulation. This would suggest that adaptive mechanisms must exist to safeguard the stability of uterine blood flow.

The large medusa of veins in the broad ligaments have been commonly referred to as depots for the accumulation of excessive amounts of blood. Undoubtedly these structures contribute greatly to the maintenance of a relative constancy in uterine venous pressure. At cesarean section these veins have a transparency and, by direct observation, it will be seen that the blood is in a state of turbulent flow. This would indicate that these vessels are capable of great accommodation, dilating and contracting at will.

In the patient at term, in the supine position, were venous blood diverted selectively into the uterine vein in any significant amount, the venous pressure in this vessel should be greater than in the femoral vein. Our group at the Boston Lying-in Hospital, utilizing the method described last evening by Dr. McCall for measuring cerebral blood flow, has made some observations of the hemodynamics of the uterine circulation. The venous pressure in the uterine vein is comparable to that of the femoral vein in the order of magnitude of 15 to 20 mm. of mercury in a patient in the supine position at cesarean section. This is strong evidence that the veins of the pelvis responsible for the drainage of blood from the uterus do expand and contract to maintain the venous pressure level at comparatively low and constant levels and thereby preserve uterine circulation.

In the light of present knowledge of the routes of maternal blood flow, it is difficult to conceive of retrograde pressure, at least within physiologic ranges, being transmitted from the inferior vena cava through the uterine vein, the substance of the uterus, and back into the intervillous space, to produce abruptio placentae. In this connection, I would hazard a guess that, in the dog, placental detachment would occur experimentally at a much lower venous pressure than presumably is required in the pregnant woman. Species differences with respect to placentation will make it difficult to interpret experimental findings in the animal with clinical fact.

Under circumstances of acute vena cava occlusion, the largest pressure component would probably be diverted into the large vessels leading to the lower extremities. Should the pressure within the vascular channels of the uterus develop an intensity which would threaten the deciduotrophoblastic junction, extensive marginal sinus rupture should coexist.

The marginal sinus, in addition to draining the bulk of the venous blood from the intervillous space, has been suggested as serving the function of a reserve safety valve to guard against any variable pressure changes of the blood within the intervillous space and its return to the uterine circulation. One might conceive that under the conditions of these experiments the "safety valve capacity" of the marginal sinus would be tested and a diffuse widespread rupture of this structure would occur. With rupture of the marginal sinus, a vent would be provided through which blood could escape and dissect and separate portions of the placenta. Through lack of morphologic examination of the placenta, one wonders if such an accident did not occur in Dr. Mengert's second case. The movies seemed to bear this out.

Otherwise we must discard the Spanner concept and assume that the bulk of the blood leaves the intervillous space through veins in the base of the cotyledons. This is not to imply that veins elsewhere in the uterus cannot bleed as a result of venous con-

gestion produced under these experimental conditions. Such a possibility may account for the free blood encountered in these uteri when they were opened and would apply particularly to the first case shown. Indeed, the blood flow through the intervillous space may be compared to the portal system in the sense that it is somewhat independent of those influences which may affect the caval blood flow contained elsewhere in the uterus.

If Dr. Mengert and his group are able by this method to produce retroplacental hematoma formation in the presence of an intact marginal sinus, the validity of the Spanner concept of intervillous blood flow will be challenged. On the other hand, perhaps Dr. Mengert has furnished an explanation as to how the syndrome of marginal sinus rupture occurs. Certainly, late pregnancy bleeding of considerable magnitude may arise from such a source without provocation. Perhaps alterations in the hemodynamics secondary to postural changes are sufficient to rupture the marginal sinus.

This work focuses attention therefore on a possible role of venous congestion in the production of placental separation in contrast to the more popular belief that arterial ischemia and decidual necrosis are the underlying defects. Further elaboration on these studies undoubtedly will reveal the exact role of the former in the possible production of premature separation.

DR. CONRAD G. COLLINS, New Orleans, La.—We have done many vena cava ligations; last week we did our ninety-ninth since 1941, when we began a study of this procedure. However, in all our cases the uterus had been emptied previously, either by abortion or by normal delivery or by cesarean section. We do have a certain number of observations which we can present this morning which may support Dr. Mengert's contentions and may not.

I know of only one case in which the vena cava was ligated prior to delivery. I had a communication with the physician who did this in New Mexico and the case has since been reported. This patient had ligation at seven months' gestation. The course up to the time of delivery, during the delivery and the puerperium was uneventful. In Dr. Mengert's city, one of my ex-residents, Dr. V. Davidson, six weeks ago ligated the vena cava at the time of cesarean section but again the uterus was emptied before the cava was ligated. There was no abnormal blood loss in this patient and there were no other complications.

There is a good deal of blood trapped, immediately, when you ligate the vena cava in the human being. Whether or not the increased venous pressure plays a part in the production of edema we do not know, as we are a little confused because we can get a little edema with low venous pressure and none with high venous pressure. The ultimate result, due to collateral circulation, is a return toward normal.

I have asked Dr. Mengert whether or not this bleeding occurred before or after the placenta was separated. This is a conjectural matter and it is important. We can rationalize that, at the time of venous puncture, if we leave the tourniquet on, the patient bleeds, but, if a clot forms, we can raise the pressure and there is no bleeding. It is a question of whether or not the blood has clotted or there is bleeding into a pool. We do know that there is a great increase in the amount of blood behind the placenta in premature separation, and I believe the pressure in the veins of the pelvis is immediately raised by the temporary or continued interference with the blood flow through the vena cava. Therefore, whether or not he has produced true abruptio is conjectural. I do not think Dr. Mengert jeopardized the life of the mother or baby with his experiments.

DR. R. CALDEYRO-BARCIA, Montevideo, Uruguay (by invitation).—It is clear that a strong digital compression of the inferior vena cava during five minutes, by increasing the blood pressure in the intervillous spaces, will produce the premature separation of the placenta. But it does not seem very likely that in the pregnant woman the uterus compresses the vena cava with a force and duration comparable to the conditions of Dr. Mengert's experiment. Therefore, I will suggest another mechanism which has some features in common with the one proposed by Dr. Mengert.

This suggestion is based on the studies of human uterine contractility and blood circulation, which I am doing with Dr. Alvarez, in the Facultad de Medicina de Montevideo. We have recorded the pressure of the amniotic fluid in 450 women, during pregnancy and labor, in normal and abnormal conditions.[1, 4] In 30 cases, the intramuscular pressure in the uterine muscle was simultaneously recorded[2, 5] by means of several microballoons placed within the myometrium. In 5 cases, one of these microballoons was placed in the lumen of an intramyometrial vein, and the pressure exerted by the uterine muscle on the vein was recorded. The blood pressure of the intervillous spaces has been recorded in 7 cases.

In the 5 cases of premature separation of the placenta in which we have recorded the pressure of the amniotic fluid, we found[2, 5] that uterine contractility was very abnormal. The tonus of the uterine muscle was 3 or 4 times higher than in normal labor (average normal value: 10 mm. Hg.). Superimposed on this hypertonus there were contractions with an amplitude and intensity similar to those of normal labor. The marked hypertonus produces a continuous "overcompression" on the intramyometrial veins, increases the resistance to the venous outflow from the intervillous spaces of the placenta, and therefore increases the blood pressure in these spaces, and also in the intrauterine veins and capillaries.

As the pressure exerted by the myometrial contraction on the intramyometrial veins is 2 or 3 times higher than the pressure it exerts on the amniotic fluid,[3] the uterine hypertonus must produce a greater increase in the intervillous blood pressure than in the amniotic fluid pressure. When the difference between both pressures reaches a critical value, it must produce premature separation of the placenta.

The volume of blood flowing per second through the uterus is roughly proportional to the difference between the mean arterial pressure (which impells the blood) and the intrauterine pressure (which is the main resistance opposed to the blood flow.[3, 6] In cases of abruptio placentae, the uterine hypertonus by increasing the intrauterine pressure must reduce under normal values the volume of the blood flow. The resultant uterine ischemia (and hypoxia) plus the distention of the intervillous spaces may be the main cause of the continuous uterine pain felt by these patients. The hypoxia may be the cause of degeneration of the uterine muscle fibers; and increased capillary permeability (due to the hypoxia) plus increased intracapillary blood pressure (due to the compression of the intramyometrial veins) may be the main cause of the blood infiltration within the uterine muscle.

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DR. MENGERT (Closing).—I think Dr. Caldeyro's idea of hypertonicity of the uterus is very interesting. I would like to emphasize that we have made only one claim: that we used a single and a constant force on two human beings and on five dogs, and universally we came up with a constant result. We have gone so far as to assume that the two may be related.

I would like at this time to show the colored photographs of the dog experiments. The first is the dog uterus before the inferior vena cava was ligated; note particularly the veins over the surface of the uterus. Nine minutes later you see a tremendous injection of the veins. In dog No. 1 the hemostats are pointing to hemorrhage. Some of you may not be familiar with the dog placenta which is rectangular, circles the uterine tube, and has a focal concentration of pigment along the long side of the rectangle—uteroverdin.

This is dog No. 2 and here we did not flatten out the placenta. You can see this blood clot on the left side. That was subsequently detached and measured 10 c.c.

A REVIEW OF 1,000 MATERNAL DEATHS IN A RURAL STATE*

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A MARKED reduction in morbidity and mortality is seldom spontaneous and is seldom due to a single factor or circumstance. Such phenomena occur when there is a combination of sociologically conscious populace, friendly and devout legislators, financial aid, and, if fortunate, improved remedial aids.

Maternal mortality rates in North Carolina have shown a steady decline:

1932-36	71.1 per 10,000 live births
1941-45	33.0 per 10,000 live births
1949	11.8 per 10,000 live births

1951—Figures indicate further decrease in total maternal deaths with relative increase in non-obstetric causes.

North Carolina has been anxious for improved facilities for over a half century but the greatest impetus came in 1925 with the establishment of the Duke Endowment. This assured financial aid for indigent patients, help in hospital construction, and the beginning of an independent four-year medical school and teaching hospital.

The enactment of the Hill-Burton Bill by Congress was the next enabling factor. This is clearly demonstrated by the fact that 60 per cent of the hospitals built with Hill-Burton funds are in rural areas, and North Carolina is the largest rural state in the Union. Another pertinent fact is that these hospitals must provide for both white and nonwhite sick; and this in a state that has the second largest Negro birth rate and fourth largest Indian population. In 1924 there were 2,186 hospital beds in the State, in 1947 there were 9,635, and at present there are 13,700.

In 1945 a statewide "Good Health" program was authorized by the Legislature and supported by the State Medical Society and a large group of interested laymen. At that time the State was forty-fifth in doctor-population ratio, forty-second in hospital bed population percentage, and forty-first in maternal mortality. At present the doctor percentage has increased to thirtieth and the hospitals and health centers have increased 71 and 35 per cent, respectively. All of these new units have accommodations for maternity patients and the maternal mortality position has improved to thirty-fifth in the list of states.

	HOSPITALS AND CENTERS	BEDS	BLOOD BANKS
1924	71	2,186	0
1947	115	9,636	9
1952	248	13,700	52

*Presented at the Seventy-sixth Annual Meeting of the American Gynecological Society, Lake Placid, N. Y., June 15 to 17, 1953.

The present Maternal Mortality Committee was established in 1946. It has no legal authority and has no paid "workers." Its duty is to analyze death records, assemble all possible information, and attempt to recommend possible remedial measures. It recognized the valuable contribution such groups had made in reducing maternal mortality in other areas. The criteria it set were more stringent than those in use by the Federal agencies; hence our figures are higher. It was felt that the greatest good could come from rigid rules. This has penalized the doctors, but has given scrupulous information. Incidentally, the specialists in the centers have been given more minute inspection and more pointed letters than the general physicians working under less favorable circumstances. Mauzy[1] has given an analysis of this committee's report on the first 1,000 deaths that were reviewed.

TABLE I. MATERNAL MORTALITY IN NORTH CAROLINA, 1946-1950
1,000 MATERNAL DEATHS

CAUSE	NUMBER	PERCENTAGE
Toxemia	264	26.4
Hemorrhage	259	25.9
Embolism	74	7.4
Infection	73	7.3
Cardiac disease	64	6.4
Anesthesia	25	2.5
Other obstetric	103	10.3
Nonobstetric	112	11.2
Insufficient information	26	2.6
	1,000	100.0

The plan as outlined by the committee is: The Bureau of Vital Statistics will look up a birth certificate which was filed six months or less before the death of the mother. Because of the alertness and efficiency of this Bureau, the committee's figures on North Carolina's maternal mortality are somewhat higher than those compiled by the Federal Government.

A standard questionnaire is mailed to the physician signing the death or birth certificate (or both) in every case of a maternal death. Occasionally no reply is received from the physician, and the questionnaire must be sent to the public health officer, a near-by member of the committee, or the local medical society. Generally speaking, this questionnaire supplies all the information necessary for the analysis of a case. Occasionally it is necessary to send questionnaires to various consultants.

The question of preventability is often discussed. The committee has followed this rule: As a part of the analysis of every case, the committee decides whether or not they feel that the death was preventable. It should be emphasized that this decision is made on the basis of the "ideal" situation. In other words, a maternal death is considered preventable if it "probably" could have been avoided by the application of ideal standards of medical care. In those cases which are considered preventable, the responsible factor in preventability is sought. One such factor is assigned to each case—physician, patient and/or family, midwife, or facilities. If the responsible factor lies with the physician,

it is further subdivided into the four factors of diagnosis, judgment, technique, and management. In cases where multiple factors were involved, the committee selected the one which seemed most directly responsible for the patient's death.

PREVENTABLE FACTOR: PHYSICIAN	
Hemorrhage	184 of 259
Toxemia	127 of 264
Infection	34 of 73
Anesthesia	25 of 25
Embolism	25 of 74
Cardiac	19 of 64
Other obstetric causes	51 of 103
Total	465 of 862

Sometimes there is confusion and correspondence with doctors regarding "terms." The committee has this definition of terms: A maternal death is defined as any death, regardless of cause, occurring during pregnancy, or within six months after the termination of pregnancy. This includes any death due to homicide, suicide, accident, or disease not even remotely connected with pregnancy. All maternal deaths are divided into "obstetric" and "nonobstetric" deaths. A "nonobstetric" death is one in which the major cause of death is in no way related to the pregnancy. A death is considered "obstetric" if the major cause of death falls into any one of the following three general groups:

1. Direct obstetric complications, such as abortion, ectopic pregnancy, hyperemesis, postpartum hemorrhage, toxemia, pulmonary embolism, and anesthesia.

2. Diseases which are aggravated by the physiologic changes in the demands of pregnancy, such as renal or hepatic disease, tuberculosis, and pneumonia.

3. Diseases which lead to obstetric complications or necessitate obstetric intervention, for example, acute peritonitis following appendicitis leading to abortion or premature labor.

OTHER OBSTETRIC DEATHS	
Tuberculosis	26
Acute yellow atrophy	14
Peumonia	9
Puerperal accident	8
Shock due to exhaustion	7
Appendicitis	7
Intestinal obstruction	6
Peritonitis	4
Transfusion reaction	3
Pyelonephritis	3
Amniotic embolism	3
Poisoning due to abortifacient	3
Diabetes	3
Chorionepithelioma	2
Sagittal sinus thrombosis	1
Influenza	1
Ruptured hemorrhoidal varix	1
Drug sensitivity	1
Pyelophlebitis	1
Total	103

Each of these deaths was scrupulously analyzed and we believe correctly classified.

Donnelly[2] has studied these figures from many approaches and a tragic fact has been the associated fetal wastage. One of the biologic functions of the mar-

ried women is that of reproduction, yet this analysis reveals 844 obstetric deaths and associated with this maternal loss is a fetal salvage of only 49 per cent not including neonatal deaths. Thus the loss is compounded.

TABLE II. FETAL SALVAGE, 882 PATIENTS

CAUSE OF DEATH	FETAL LOSS	FETAL SALVAGE	FETAL SALVAGE PERCENTAGE
Toxemia	122	142	53
Hemorrhage	172	87	33
Embolism	27	47	60
Infection	71	2	3
Cardiac	25	39	61
Anesthesia	10	15	60
Other obstetric causes	50	53	51
Total	477	385	49

There were 259 deaths from hemorrhage. The usual background of placenta previa, abruptio placentae, ruptured uterus, interference, and abortion follows orthodox figures but analysis of 33 deaths from ectopic pregnancy is revealing. Twenty-three patients were not operated upon and only one patient had any type of accessory examination for diagnosis and this was a curettage. Only 81 patients in this hemorrhage group had any blood at all. This omission is better understood when it is shown that all but 9 of the 52 blood banks in this state were started after 1947; yet the first blood bank in America was established at Salisbury, N. C.

The 264 deaths (26.4 per cent) from the toxemias and renal diseases simply confirm what has been written over the years regarding this miserable preventable complication which is rampant in this area. Equally significant, the toxemias were thought to be a contributing factor in 93 cases in which the primary cause of death was listed in some other category. The 73 deaths from "puerperal infection" also reflect the influence of poverty, malnutrition, anemia, and the inability of the "medically inarticulate" to avail themselves of even obvious and ready aid. They also point to the increasing abortion rate in the nonwhite.

During the years 1946 through 1950 there were 532,310 live births. The midwife delivered 2.7 per cent of white and 35.9 per cent of nonwhite mothers in North Carolina. Though we know of the large numbers of mothers cared for by these people, there is a certainty that we have not helped them and used them in a thoroughly intelligent manner. They are sensitive. They have unbounded confidence in their own ability and any criticism or suggestion of criticism is likely to lead to sullenness, anonymity, or even chicanery. Our best approach is through the County Health Department. Millen[3] has made this observation:

> It has been my experience that when there is an inferior method working in the same area where a superior method exists, the inferior one is much worse than the method in some areas where there is no better method. In other words, I think that the midwifery Kosmak speaks about for the remote parts of our country where there are no doctors is one thing, but midwifery in counties where there are good doctors usually means that both the midwife and the people who use them are really having the shrouds pulled in over their heads because it is only the worse kind of midwife who would tend to play second

fiddle. I was rather struck, when I was abroad this summer visiting in some hospitals, by finding that the gynecological aspect of English medicine is remarkably good but the delivery by a midwife was below what we would accept here.

TABLE III. MORTALITY RATES AND PLACE OF DELIVERY IN REPRESENTATIVE STATES FOR 1949 (MAUZY—1949)

STATE	PERCENTAGE NONWHITE	TOTAL DELIVERIES	MORTALITY (PER 10,000 LIVE BIRTHS)	DELIVERY (PERCENTAGE)		
				HOSPITAL	M.D. AT HOME	MIDWIFE
North Carolina	32.9	35,555	21.7	35.0	30.0	35.0
Mississippi	56.2	37,318	30.8	17.0	21.0	62.0
District of Columbia	41.3	8,190	8.5	97.0	3.0	0.0
Illinois	10.0	18,917	12.1	78.0	21.0	1.0
Pennsylvania	7.5	16,861	16.0	91.0	9.0	0.0
New York	8.8	26,504	20.8	96.0	3.0	1.0
California	8.3	20,414	13.7	9.0	3.0	1.0

Mauzy[1] collected data from diverse geographic areas in the United States on nonwhite maternal deaths. The totals were sufficient to be statistically sound and the division into home, hospital, physician, and midwife deliveries gives interesting and helpful information. In North Carolina during the year's study there were 35,555 nonwhite deliveries, only 35 per cent of which were in hospitals and the mortality rate was 21.7 per cent. In a large northern state there were 26,504 such deliveries, 96 per cent of which were in hospitals and the mortality was 20.8 per cent. New England, the northwest, and west central areas are not included because of the very low nonwhite population, as is shown in the following tabulation.

PERCENTAGE OF NONWHITE POPULATION IN THE UNITED STATES AND EACH GEOGRAPHIC DIVISION, 1950

(Population enumerated as of April 1)

UNITED STATES	11.0
New England	2.0
Middle Atlantic	7.0
East North Central	6.5
West North Central	3.5
South Atlantic	24.0
East South Central	23.0
West South Central	16.5
Mountain	5.0
Pacific	6.0

If one transposed the United States maternity mortality statistics to this tabulation it would become immediately evident that the highest maternal mortality is in the highest nonwhite areas. Is this a simple coincidence? Do pellagra and toxemia simply parallel each other? Do the placenta, the pituitary, and the ovary in the female in New England differ from that of the female in Alabama? Temperature, weather, rain fall, humidity, and other regional and seasonal variables have been duly recorded without conclusive evidence. Are vitamins an exogenous hormone? If not, can the bodily economy maintain an adequate hormone level without penalizing the female living on a "Goldberg diet"? We have seen and recorded the paradox of maternal mortality, especially the toxemia deaths, in relation to the economic fluctuations. In the "lean years" when cotton and tobacco are not profitable

the rural dwellers and "share croppers" do have a vegetable garden, cow, and chickens. They are on "relief" and are eating more wisely. The death rate is lower. In the "years of plenty" all hours and interest are devoted to the "cash crop." The county store or commissary substitutes for the garden and salt pork ("fat back"), molasses, and corn meal are the stomach-satisfying articles of diet and the energy-producing factors. Rancid fat is not considered a vitamin-negating substance, nor soft sweet carbonated drinks a remarkable substitute for citrus drinks. The triad of "ill housed, ill clothed, and ill fed" is deep in the feeling, and we hope understanding, of the South. They are now becoming increasingly manifest in the metropolitan areas, where citizens of the United States are flocking and a shift in population trend is evident. The hospital facilities, providentially, are better and the economic dietary habits are more favorable. Day-old white bread, slightly blighted vegetables, fish, and other such articles are readily available at a reduced cost. Thus the defenses against fetal wastage, toxemia, infection, and hemorrhage are fortified and should be reflected in more favorable statistics in these areas.

MATERNAL DEATHS

Indigent-Private Patient Ratio.—	
Toxemia	
Hemorrhage	
Infection	2:1
Private Patient-Indigent Ratio.—	
Embolism	48:26
Anesthesia	15:10

We were interested in the major cause of death in the so-called "indigent" and "private" groups. Some of the data are of such small totals that, statistically, they are nonconclusive. Toxemias, hemorrhage, and infection do stand out in the indigent group. Heart disease, to a lesser degree, comes in this category. The relative number of deaths from embolism and anesthesia is small but the majority do fall in the private group. It is difficult to disassociate embolism from infection and it is extremely difficult definitely to certify this cause of death. However, we did find a relative proved increase in the "private" group. The anesthesia deaths were carefully scrutinized. At present our State group of anesthetists is undertaking a survey of all anesthesia deaths in detailed fashion. Nine of the patients had surgical doses of spinal anesthesia and the uniform remark was that the obstetrician had to give the spinal anesthesia because an anesthetist was not available. None had chloroform.

Since the detailed analysis, including I.B.M. punch card recording, of the first 1,000 deaths was completed in 1950-1951, the committee had an additional 400 charts which have been reviewed but not finally classified. It is gratifying to note an indication that the maternal death-live birth ratio has further decreased and the nonobstetric causes are more evident. It is a source of enormous satisfaction to know that the general physicians, hospitals, agencies, and specialists are cooperative and apparently feel no animosity toward a committee that has been motivated medically by altruistic objectivity. Under such circumstances the committee can label a death "physician responsibility"

if there is a single factor that might have altered the patient's downward course after she was first seen by a physician. We now consider secondary highways, all-weather rural roads, improved farming methods, communications of all sorts of equal importance as Board certification and Federal grants. Most reports agree that once a patient reaches a hospital she will receive good treatment. We have missed the grandparents, but we do have the grandchild.

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Discussion

DR. S. LEON ISRAEL, Philadelphia, Pa. (by invitation).—It is a privilege to open the discussion upon Dr. Ross's frank, illuminating analysis of 1,000 maternal deaths in a rural state. He has highlighted, quite boldly, the apparent fact that maternal mortality bears a direct relation to the socioeconomic standards of a community. His critical sifting emphasizes once again that the three horsemen who carry death to parturients—toxemia, hemorrhage, and infection—ride twice as frequently among the indigent. Happily, however, Dr. Ross's report also has a brighter side. North Carolina, keeping pace with its sister states, has harvested a shorp drop in maternal mortality during the last two decades.

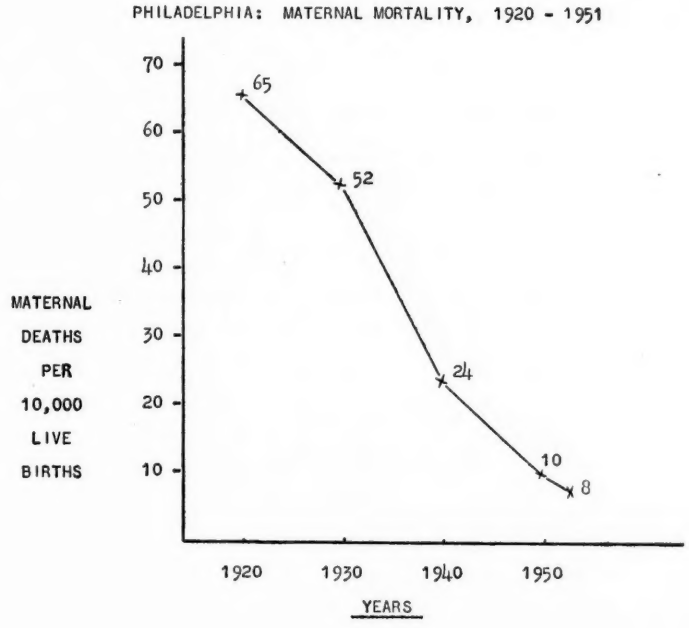

Fig. 1.

The factors responsible for the countrywide betterment include improvement training of medical and nursing personnel, the ready availability of blood transfusion, anesthesiology, the use of antibiotics, better obstetric technique, clearer evaluation of the nutritional aspects of pregnancy, and the smooth functioning of local maternal mortality committees. The last mentioned is deservedly credited in the North Carolina report.

The provocative statement by Dr. Ross anent the shift of nonwhite population from rural to metropolitan areas stimulated me to compare the maternal mortality in North

Carolina with that of Philadelphia, a highly industrialized city which also boasts of an efficient maternal mortality committee. It is most agreeable to learn that Philadelphia's experience supports the contention of Dr. Ross that the northward shift of nonwhite population is counterbalanced by adequate hospital facilities and a beter dietary. As shown in Fig. 1, the maternal mortality in Philadelphia has also declined sharply. It is of equal interest to study the most recently computed annual rate, that for the year 1951, which is summarized in Table I. Quite apparent therein are two items of interest, namely, that the ratio of white to nonwhite births approximates that of North Carolina and that hospital deliveries are the rule. The similar percentage of nonwhite parturients makes it possible to contrast the maternal mortality of Philadelphia and that of North Carolina, as expressed in Table II. The lower mortality in Philadelphia, in spite of the comparable 30 per cent ratio of nonwhite deliveries, must be attributed to the high incidence of hospitalization, the excellence of which is owed—at least in part—to the forceful leadership of the maternal mortality committee during the past 20 years.

This brings me, finally, to agree with the inescapble conclusion of Dr. Ross that better roads, improved planting schedules, and more hospitals will lower further the maternal mortality of any rural area.

TABLE I. PHILADELPHIA, 1951

Population:		2,092,241
Total births:		50,318
White:	38,917	
Nonwhite:	11,401 (30%)	
PLACE OF DELIVERY	WHITE	NONWHITE
Home	2%	5%
Hospital	98%	95%

TABLE II. NONWHITE DELIVERIES, NORTH CAROLINA AND PHILADELPHIA

PLACE	PERCENTAGE NONWHITE	TOTAL DELIVERIES	PERCENTAGE HOSPITAL	MORTALITY PER 10,000 LIVE BIRTHS
North Carolina	32.9	35,555	35.0	21.7
Philadelphia	30.0	11,401	95.0	8.0

THE NONOPERATIVE TREATMENT OF STRESS INCONTINENCE IN WOMEN*

LAWRENCE R. WHARTON, M.D., BALTIMORE, MD.

IN THIS study, it is my purpose to discuss only two features of the problem of stress incontinence—the clinical findings and the result of nonoperative treatment in a series of 63 cases.

My interest in the nonoperative treatment of stress incontinence dates from the publication of Kegel's first paper on this subject in 1949. Shortly after that, I began to study these cases clinically, to determine any factors that might contribute to this syndrome or be associated with it. At the same time, an effort was made to eliminate these various factors and to observe the effect of this therapy on stress incontinence.

This series includes 63 cases of stress incontinence, most of which have been studied in the last three years. All but three of these women were my private patients—two were ward patients from the Johns Hopkins Hospital and one a ward patient from the Women's Hospital of Baltimore. I hereby acknowledge my indebtedness to Dr. Richard Te Linde and Dr. Leo Brady, respective chiefs of these services, and to their house staffs for the privilege of including these three patients.

In this summary, I shall present first the clinical data, outlining the various medical, gynecological, urological, neurological, psychic, or other factors that we found in these cases. The effect of the treatment of these conditions on stress incontinence will then be summarized, and conclusions presented.

Clinical Data

Age.—These women were in the following age groups:

20-30 years	4	60-70 years	11
30-40 years	7	80-90 years	5
40-50 years	16	90 years+	2
50-60 years	18		

Parity.—Fifty-three of these women had borne children, 10 were nulliparous.

Duration of Incontinence.—

One year or less	17	15 to 25 years	6
1 to 5 years	13	25 to 40 years	6
5 to 10 years	8	40+ years	3
10 to 15 years	10		

*Presented at the Seventy-Sixth Annual Meeting of the American Gynecological Society, Lake Placid, N. Y., June 15 to 17, 1953.

Obesity.—Twenty-seven of these patients were moderately or markedly obese.

Nervousness and Psychic Instability.—This was a definite factor in this series of cases, and seemed to play a considerable role in the end result of treatment. This will be discussed in the section on end results.

Urinary Disorders.—In this group, the following urinary disorders were found:

Cystitis, trigonitis, and urethritis	11 cases
Hydronephrosis, not infected	2 cases
Hydronephrosis, infected	1 case
Urethral caruncle	1 case
Vesicovaginal fistula, following urethral diverticulum	1 case

Neurological Paralytic Diseases.—Two of these patients developed paralysis of the urinary and rectal sphincters, after having been treated with fair success for stress incontinence. This complication vitiated any benefits that the former treatment may have conferred.

Childbirth Injuries.—In 28 cases, the stress incontinence was associated with prolapse of the uterus, prolapse of the vagina, or cystocele. In 14 of these, the childbirth injury was successfully corrected, and the effect of these operations on stress incontinence will be presented. Also, in 8 instances, the childbirth injury was not operated upon at all; in 6 cases, stress incontinence appeared for the first time within 2 weeks after a successful correction of prolapse. All of these cases were treated by exercises.

The Kelly Plication Operation.—In four instances, in addition to operations for prolapse, the Kelly plication operation was done for associated stress incontinence. Since the incontinence persisted after this operation, they are included in this series, and the effect of exercises is observed.

Stress Incontinence Without Demonstrable Pathologic Disorder.—In 26 patients, there was no demonstrable disorder in the pelvis or the urinary tract. Quite a few of these persons traced their loss of control to childbirth; in none, however, was there any significant cystocele, rectocele, or descensus—at least none that warranted surgical treatment or caused symptoms. A few of these patients were moderately obese, but not to a pathological extent.

Results of Treatment

Urological Treatment.—In this group there are 13 with stress incontinence who were treated for various urological conditions. The summary of this treatment follows, especially in relation to its effect on stress incontinence.

	NO. CASES	UROLOGICAL RESULT			EFFECT ON STRESS INCONTINENCE		
		WELL	IMP.	FAILED	WELL	IMP.	FAILED
Cystitis, urethritis	10	7	1	2	2		4
Pyelonephritis	1		1				1
Hydroureter	1	1			1		
Urethral caruncle	1	1					1

The effect of the urological treatment is clear. Considering all these disorders together, it appears that the urological disease was eliminated in 9

patients, improved in 2, and not relieved in 2. In 3 of these, the stress incontinence was also eliminated at the same time, in 6 the urological treatment had no effect on the stress incontinence. In 4, the result was confused because the patients received both urological treatment and exercises at the same time.

In 9 patients who received urological care and whose stress incontinence was not relieved by it, we recommended exercises. In this group, 3 were improved, 3 were cured, and in 3 the result was a failure. In 2 of these, the cause of failure was the fact that the patient did not use the exercises. In the third failure, the patient was over 70 years old, had had recurring cystitis for many years which we could not eliminate, and had had stress incontinence for over 40 years. Although she used the exercises faithfully, she failed to show any improvement in urinary control.

In summarizing our experience with urological diseases and stress incontinence, it seems that the elimination of a urological disorder may in some cases also eliminate accompanying stress incontinence. It usually improves urinary control. However, in some cases, urological treatment had no effect on stress incontinence. In most of these cases in which the urological treatment failed to eliminate the stress incontinence, exercises have been helpful.

Exercises in Cases of Prolapse and Stress Incontinence

In this group we have 28 patients in whom the stress incontinence was in some way or other associated with uterine or vaginal prolapse or cystocele. We are including uterine prolapse only of second degree or more, and only cystoceles that protruded from the vaginal orifice or filled it. In general, these cases fall into three groups:

Group I. Patients with both prolapsus and stress incontinence in whom the stress incontinence persisted after the surgical cure of prolapse. 14 cases.

Group II. Patients with both prolapsus and stress incontinence who were not operated upon but treated only by exercises. 8 cases.

Group III. Patients with prolapsus who did not have stress incontinence till after the successful surgical correction of the prolapsus. Postoperative stress incontinence. 6 cases.

Group I.—This includes 14 women with prolapsus who had also stress incontinence; they were all operated upon successfully and the prolapsus was cured. These operations were done by various gynecologists, including myself. In 4 of these cases, Kelly plication of the urethral sphincter was also done. In only 2 of these 14 patients did the surgical procedures have any effect on the stress incontinence, and these showed only moderate improvement. One of these who showed improvement had had a Kelly plication of the urethra. In the remaining 12 (3 of whom had also had Kelly plication operations) the stress incontinence was not affected by these procedures.

This group of cases brings to our attention the fact that the successful correction of prolapse does not always eliminate an associated stress incontinence. Undoubtedly, there are many instances in which that has occurred; otherwise the idea would not be prevalent among gynecologists. Also, this

small group is not an indictment of the Kelly plication operation, for, as Te Linde has pointed out, in our clinic it has been a fairly dependable method of correcting stress incontinence. This group merely includes an unfortunate number in whom these procedures failed to cure stress incontinence.

We recommended exercises for all of these 14 women. In 13 cases, the results are as follows:

Cured by exercises	5 cases
Improved by exercises	3 cases
Failed	5 cases

The failures were due to neurological paralysis of the sphincters of the urethra and rectum in 2 cases and subsequent paralytic disease; 2 women failed to take the exercises; and in one the faithful use of exercises has yielded no benefit as far as urinary control is concerned. It therefore appears that in this group exercises have been definitely helpful. In 4 of these 13 cases, the failure was unavoidable, either because of the unwillingness of the patient to cooperate or because of subsequent neurological developments.

Group II.—These 8 women had various types of childbirth injury, varying from rectoceles and cystoceles of moderate size with second-degree prolapsus to complete procidentia. For various reasons, none of them was operated upon, but all of them were treated by exercises. The results were as follows:

Cured	6 cases
Improved	2 cases
Failed	0 cases

One striking instance may be mentioned: A woman 74 years old who was admitted to the public ward of the Women's Hospital with complete prolapse of the uterus and vagina had had the prolapse so long that she had become accustomed to it. However, her chief complaint was the stress incontinence that had been present for two years.

As is customary with elderly patients who are not particularly good surgical risks, she was kept under observation for a few days. During this time she developed a coronary thrombosis, which completely canceled any idea of surgical procedure. She was therefore given a course of exercises, which strangely enough afforded her complete urinary control. At the present time, one year later, she still has no stress incontinence, even though she wears no pessary.

Group III.—This group consists of 6 patients who developed stress incontinence after having been operated upon for uterine or vaginal prolapse or having had some other vaginal operation.

This is a rather disconcerting and disappointing sequel to a surgical operation that has been otherwise completely successful. Generally, the incontinence develops immediately after the operation.

Fortunately, in all but one of our 6 cases, the postoperative stress incontinence has been either cured or improved. In 4 cases, relief followed exercises; in one case, it disappeared spontaneously without any treatment. This patient was operated upon before the era of exercises. In one instance, we

are recording the result as a failure, although the exercises have not had a fair trial. The patient has not used them as directed.

One rather unusual case of postoperative stress incontinence was observed in a woman 37 years old. She had had a urethral diverticulum which had been operated upon in 1951. This was followed by a vesicovaginal fistula, which was operated upon one month later, without success. The surgeon then sent this patient to Baltimore, where she was admitted to the public ward of the Johns Hopkins Hospital. The resident gynecologist located the fistula, and also observed that the urethral sphincter was very weak, permitting stress incontinence. He operated upon her, closing the fistula and plicating the urethral sphincter. The result of the fistula operation was perfect; however, she was almost as incontinent as before because of the weak sphincter. He therefore recommended exercises, which proved completely successful and restored perfect urinary control.

In summary, then, this experience with stress incontinence and prolapse leaves one in a quandary. The explanation will depend upon one's views. It seems clear that stress incontinence is not entirely dependent upon the position or level of the bladder, urethra, or pelvic organs. It has occurred in many women who had prolapsus of varying degrees, and has persisted after the prolapsus had been corrected. Likewise, it has been corrected by exercises in women with prolapsus, even though the prolapsus has not been treated in any way. Also, it has been produced by the surgical correction of prolapse when it did not exist before, and, in such cases, has been improved or cured by exercises.

It is our impression that the exercises strengthen the muscles that control vesical function, and thereby improve that function. We have not been able to observe that these exercises have affected the cystocele or lessened the degree of prolapsus, although some patients have volunteered the information that they feel more support and strength in the pelvis and lower abdomen than they did before using the exercises.

General Summary.—In general, in 63 cases in which follow-up records are satisfactory, the results of exercises have been as follows:

Cured	30 per cent
Improved	51 per cent
Failed	19 per cent

It is our impression that the division between these groups is neither hard nor fast nor possibly permanent. Thus, a woman may have no stress incontinence for six or more months after the use of exercises; then, because of some nervous disturbance, strain or illness, she may have a return of leakage. Generally, these persons have learned the value of exercises and resume them with benefit, without consulting the gynecologist.

Also, it is possible that the benefit obtained by exercises may not be as lasting as that obtained by surgery. Again, however, this is only a conjecture. One thing is certain—not one of the patients who have found benefit by simple exercises would for a moment entertain the idea of surgery.

Causes of Failure

The causes of failure are nervousness, failure to take exercises, obesity, neurological disease, urological disease, senility, and long duration of stress incontinence.

Nervousness has a great deal to do with urinary function and control. In borderline cases, a nervous upset may also upset urinary control, as many patients have told us. One woman has stress incontinence only when she is in town in the midst of her domestic and business turmoil. When she is out of town, she never thinks of her bladder. In such cases, the judicious use of a mild sedative or hygienic instruction and reassurance may be helpful.

A considerable number of our failures occurred in women who were too lazy or disinterested to try the exercises. They would rather be wet than weary.

Obesity is a factor in some persons. At times, in obese persons, the use of a tight corset increases the pelvic pressure and makes stress incontinence worse. Very seldom, however, do women find it convenient to reduce their diet.

Neurological disease may completely destroy urinary and rectal control. This happened in two of our cases.

Urological disorders, especially urethritis, cystitis, and trigonitis, make it difficult to manage stress incontinence. We have found that in a few cases incontinence may be eliminated by treatment of urological disease; generally, however, the result is an improvement which can be further helped by exercises.

Senility and *chronicity* often go hand in hand. This was observed also by Kegel. In our experience, it is sometimes impossible to re-educate the sphincter muscles in a woman over 80 or 90 years old, or in a woman who has had incontinence for 40 or 50 years. In such cases, one must overcome not only inherent muscular weakness and atrophy, but also overcome mental inertia and habit formation.

The Nature of the Exercises

The exercises are those described by Kegel. They consist merely in the voluntary and strong contraction of the muscles that stop or prevent the flow of urine. It is at times difficult, almost impossible, to convey this idea to some patients. They are instructed to make the same effort that they do when they prevent the flow of urine, if they should have the desire to void under unpropitious circumstances. This contraction also involves the vaginal muscles and rectal sphincters.

This exercise should be repeated 15 times, three times a day. Generally, within one month, benefit is evident.

The Perineometer.—We have not used the perineometer devised by Kegel, and find our results comparable with his. It is our opinion that the perineometer is an unnecessary encumbrance; furthermore, in a virgin or following a tight perineal repair, it would be impossible to insert the rubber bulb into the vagina. Without the perineometer, the exercises can be carried out wherever the patient happens to be and without any inconvenience.

Conclusions

The Role of Exercises in the Treatment of Stress Incontinence.—From this experience, it appears that exercises are a distinct adjunct in the treatment of stress incontinence. In summary, they have proved useful in the following situations:

1. If a woman has prolapse or any definite gynecological disorder which requires surgical treatment, and also has stress incontinence, we think the indicated gynecological operation should be performed. At the same time, a suitable operation may be done to correct the stress incontinence. If the patient continues to have stress incontinence after this treatment, exercises should be used.

2. If a person with stress incontinence and prolapse cannot be operated upon, the stress incontinence may be treated by exercises.

3. If stress incontinence develops after an operation, exercises have been useful.

4. In urological conditions complicated by stress incontinence, exercises supplement urological treatment.

5. Other factors are also worth consideration in treating stress incontinence—obesity, nervousness, and worry.

The simplicity of this method of treating stress incontinence recommends it. Exercises cannot possibly do any harm; they involve no expense or inconvenience. If they fail, nothing is lost; if they succeed, an operation may be avoided.

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Discussion

DR. ERLE HENRIKSEN, Los Angeles, Calif.—In early 1948, Kegel requested permission to start a stress incontinence clinic on the gynecologic service of the University of Southern California. Being surgically minded, I was very skeptical of his almost miraculous claims and placed the request in my deepest file. Three months later, one of my patients, on whom I had operated six years before with the intent of curing her stress incontinence, reported that she had been cured by vaginal muscle exercises. This patient had also had surgery for the incontinence in New York and in Boston. The results following each of the three operations were identical, i.e., relief for four to six months, then dribbling. When the patient left the office I immediately called Dr. Kegel and told him to

start the clinic. I am certain that those of you who have visited our clinic appreciate the continued enthusiasm for the nonsurgical treatment of stress incontinence in women.

With direct questioning, the incidence of incontinence in both clinic and private patients is surprisingly high. Many women accept this disturbing nuisance as the price for parity, advancing age, and menopause. Because of the attendant embarrassment they need laugh or cough in solitude. Repeatedly I have been impressed with the degree of discomfort and embarrassment many women will endure before seeking assistance.

Awareness of the function of the vaginal muscles is not a recent advent. At the turn of the century many physicians advised the "winking exercise" as an important part of the postpartum care. Then came the era of surgery with a world-wide race to develop a surgical procedure for the cure of stress incontinence. In the rush for the spectacular, the importance of function of the vaginal muscles was forgotten. The knife was king, ingenuity and dexterity the queen.

In our clinic we have attempted to separate the cases of incontinence into two major groups, i.e., the urgency type and the stress type. Since it is not uncommon to have both types presenting in the same patient, it is important to study the urinary tract in every case of incontinence.

I cannot agree with the statement that we are left in a quandary as to the relation of incontinence and prolapse and the answer is dependent upon one's views. Certainly any procedure, be it surgical or nonsurgical, that permits the restoration of an affected portion of the body to a normal or near normal physiologic status admits to little argument.

Several points have been mentioned that deserve repeating. First, the excellent results in those cases in which surgery was considered contraindicated. If this be true—and our experience is in complete agreement—why is it not both logical and good medical practice to place all cases of stress incontinence on this type of treatment before considering surgery? Second, the excellent results in those cases developing stress incontinence following vaginal surgery. The incidence of humiliation to the ego of the surgeon with this type of complication will be exceedingly rare if all cases of contemplated vaginal surgery are instructed in vaginal muscle awareness prior to surgery. Unfortunately, from the economic viewpoint of the surgeon, some of these patients are so improved subjectively that they have little desire to return for surgery.

The success of this form of treatment cannot be handed out on a printed form or relayed by the office nurse. To sell the idea of patient-cure-thyself, the doctor must not only fully understand the principles underlying the treatment, but have faith in its value. The patient must also appreciate the plan and the principles of the treatment. Some patients possess an awareness of the function of the vaginal muscles and are able to carry out the active exercise once they have been carefully instructed. The patients lacking this initial awareness of function require repeated instructions and demonstrations. It is in this group that the perineometer often proves invaluable.

Despite everything, however, an occasional patient will rather continue damp than expend the exertion required for the few minutes of daily exercise. This, being a male, I cannot fathom.

The nonsurgical method of treating this very disturbing problem is not intended completely to replace the surgical approach. There is the relatively infrequent case that can be cured only by the right type of operation. It has also been noted that the exercise, instituted both before and after parturition, is a very valuable aid in preventing the unilateral and occasional bilateral atrophy of the pubococcygeus muscle that may follow birth trauma. Also, in cases of abdominoperineal resections, the frequent complication of stress incontinence can usually be controlled by muscle education.

In closing, may I present a table listing our results in 201 cases of stress incontinence followed two or more years. "Good" results are based on the patient's statement that she is dry and happy.

TABLE I. STRESS INCONTINENCE

	TOTAL	GOOD	POOR*	SURGERY†
Group I (on sneezing, etc.)	75	61	11	3
Group II (on standing)	61	55	6	0
Group III (continuous)	59	39	15	5
Group IV (complete)	6	2	3	1
Total	201	157‡	35	9

*Poor: 19 cases with complications, i.e., neurological, surgery, etc.
†Surgery: 7 cases considered surgical after preliminary studies.
‡75% uncorrected; 88% corrected.

Thus we feel sincerely justified in our continued support and acclaim of this form of treatment for stress incontinence. It is our weighed opinion that, in the practice of good medicine, few patients with incontinence should be subjected to the surgical approach without every effort being made to cure them without surgery.

DR. HOUSTON S. EVERETT, Baltimore, Md.—I was asked originally to be the official discussant of this paper, but I felt that it was much better for Dr. Henriksen to do this, as he has probably had much greater experience with this method of treatment than any of the rest of us here. I want to point out that in 3 or 4 cases Dr. Wharton stated cure was brought about by urological treatment alone. I feel that most of us make the mistake of not differentiating clearly between stress and urge incontinence. The differentiation between these two types of incontinence can usually be made while you are talking to the patient. The patient with true stress incontinence has no other symptoms except that of the loss of urine. With urge incontinence on the other hand, when the patient feels the desire to void it is so urgent that she often cannot reach the bathroom before there is loss of urine. In urge incontinence there is a much more real diagnostic problem than in stress incontinence because the former type may be due either to neurological or urological disease. I believe that those patients mentioned by Dr. Wharton in whom the incontinence was relieved by urological treatment were suffering from the urge type resulting from urological disease rather than from stress incontinence.

The patients with neurological disease as a basis for their incontinence present the greatest therapeutic problem and usually cannot be cured. The two commonest types of neurological disease which produce this condition are spina bifida occulta and multiple sclerosis. These people have small spastic bladders, and about the only thing that can be done in the way of therapy is the use of antispasmodic drugs, which will usually relieve the symptoms in varying degrees but will in no way relieve the condition.

Many of the urological conditions which lead to urge incontinence can be helped or even cured. My old chief, Dr. Guy L. Hunner, used to say that the most common cause of incontinence was ureteral stricture. I have never subscribed completely to his ideas as to the frequency of this entity but we do see incontinence occasionally resulting from obstructive lesions in the upper urinary tract. We had one patient with urgency and frequency to the point of incontinence who had a ureteropelvic junction obstruction without any evidence of disease in the lower urinary tract. At operation the obstruction was found to be due to both an aberrant vessel and a congenital stenosis. The vessel was ligated and divided and the stenosis treated by a plastic procedure on the ureteropelvic junction. The incontinence was completely relieved. Incontinence on this basis results from the anatomical mechanism of Bell's muscle, which is a continuation of the longitudinal muscles of the ureters. If the ureter is irritable that irritability continues into the trigone through Bell's muscle and the patient is likely to have urge incontinence.

One of the most difficult problems arises when both stress and urge incontinence exist in the same patient. I had a patient referred to me who had had multiple operations for

stress incontinence without relief, but her symptomatology made it evident that she also had urge incontinence. Dr. Marchetti had just come to Washington and together we did the first of his operations that I had seen. I heard later from this patient and she stated that she could laugh, jump, or cough without leaking, but when she had to void she often could not reach the bathroom.

I think, therefore, that this differentiation is important, and I believe that the three or four patients whom Dr. Wharton has described as cured by urological treatment alone were probably suffering from the urge type.

DR. WHARTON (Closing).—I have not used the perineometer. I instruct the patient to use the exercises 15 times three times a day. If she is employed, she can do these exercises regardless of where she is. Sometimes it is difficult to cure stress incontinence, either by exercise or by operation. The condition may recur, and it may recur after exercise or operation. The patient may be dry for six to eight months after being relieved by exercises, and then for some reason she may have a recurrence. If she has been cured before that by exercises, she resumes her exercises without telling anyone about it and is usually helped.

The perineometer may be helpful in difficult cases that do not yield to exercises without it. We, therefore, shall reserve its use for special cases in which it appears indicated.

THE MODERN TREATMENT OF TUBERCULOSIS AND THE GYNECOLOGIST*

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THE modern treatment of pulmonary tuberculosis has introduced problems of peculiar interest to the gynecologist. It is the purpose of this paper to discuss, qualitatively rather than quantitatively, the nature of these problems as they have been presented in Saranac Lake and to indicate our present attitude on the management of gynecological tuberculosis itself.

Our interest in the gynecological problems of the tuberculous woman was aroused a number of years ago and led, in 1933, to a study of the effects of tuberculosis itself on menstrual physiology.[1] The present study is an attempt to evaluate the effects of the modern treatment of pulmonary tuberculosis with antibiotics, pneumoperitoneum, and radical pulmonary surgery on the menstrual function and it is to be noted that all of the changes described occurred during or after these forms of treatment had been adopted and not during the preliminary period of observation. Unfortunately we were unable to obtain a sufficient number of cases that had been treated by the antibiotics or by surgery alone to be of significance in studying the effect of each on the menstrual cycle; it is necessary, therefore, to be extremely cautious in attempting to draw any conclusions as to the effect of streptomycin with or without para-aminosalicylic acid or of surgery on the physiology of menstruation.

Table I shows the results of a study on 139 women patients with pulmonary tuberculosis who had been taking streptomycin with or without PAS for at least 6 months.† Thirteen patients were eliminated because they had had a hysterectomy, had reached the menopause, or were pregnant when the study was begun. Of the remaining 126, 74 had had some type of major chest surgery (wedge or segmental resection, lobectomy, or thoracoplasty) and 26 had had pneumoperitoneum for 6 months or longer.

It will be seen from this table that after eliminating transitory changes, 71 (56.3 per cent) of these women had had some alteration in their menstrual cycles while under treatment with antibiotics, chest surgery, or pneumoperitoneum. Unlike the changes found in our previous study,[1] the incidence of these changes does not depend upon the extent of disease. It is also apparent that, with the exception of those treated with pneumoperitoneum, these changes tended toward an increased irregularity or lengthened menstrual cycle and that when a period finally arrived it tended to last a shorter time with a decreased amount of flow. Twenty of these 71 women (28 per cent)

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gave a history of one or more periods skipped under the modern regime; this may be compared with 22 per cent in the older series. Thirty-four of these women had some degree of dysmenorrhea with 11 complaining of more pain, 6 less, and 17 no change.

TABLE I

Total cases	126
No changes noted	55
Total showing menstrual changes	71

Classification of disease	Minimal	Moderately advanced	Far advanced
No. in each classification	31	60	35
No. showing changes	18	33	20

CHANGES NOTED

	CYCLE		DAYS OF FLOW		AMOUNT OF FLOW	
	LONGER	SHORTER	MORE	LESS	MORE	LESS
Minimal	7	2	1	5	3	5
Moderately advanced	10	7	9	6	7	9
Far advanced	9	4	3	5	2	10

Dysmenorrhea:	
Present in	34
No change	17
More	11
Less	6

There may well be a closer relationship between the female genital tract and the respiratory tract than we realize. The so-called vicarious menstruation as evidenced by epistaxis at the time of menstruation has long been known, as has the presence of erectile tissue in the nasal cavity. In a previous study we found that of 80 girls in whom the onset of pulmonary tuberculosis was marked by hemoptysis, the hemoptysis occurred during menstruation in 26 per cent or almost twice as often as would be expected,[1] and in the days when pneumothorax was extensively used one and one-half times as many women developed pleural effusions as men (women 70 per cent, men 53 per cent).[2] There is now evidence, moreover, that more women develop peritoneal collections of fluid during pneumoperitoneum than men, somewhere in the proportion of four or five to one.[3] In some instances, two of which are recalled vividly, menometrorrhagia from endometrial hyperplasia in a tuberculous girl and from a fibroid uterus in a middle-aged woman with bronchiectasis were accompanied by pulmonary hemorrhages until the uterine bleeding was controlled by radiation. One girl, aged 26, in the present series, who has been treated with streptomycin, PAS, tibione, and is now taking Rimifon, and who had a two-stage thoracoplasty and a lobectomy, has irregular menses with two- to three-month intervals which are interspersed with two- to three-day periods of metrorrhagic spotting that are always accompanied by streaked sputum.

Of the 74 girls in this series who had undergone some type of major chest surgery, 27 showed changes in their menses during or immediately

following the surgical procedure, which was often done in stages. It is my impression that, with the exception of gynecological surgery itself, in no other form of surgery will such an incidence of menstrual effects be found. Nine patients developed amenorrhea: 5 for one month, 2 for two months, and 2 for periods longer than two months; in one case the menses became progressively scantier after a lobectomy and thoracoplasty in 1951 until amenorrhea that lasted four months ensued; the periods then returned but with an additional day of flow. Four patients had their periods a week early during or just following chest surgery and one patient had her menses delayed a week. Another patient began to menstruate every two weeks and flowed for two weeks for several months following her operation; she then reverted to a thirty-day cycle but with an increased number of days of flow, and finally ended up with her old schedule. Following a second two-stage operation six months ago she again began to flow every two weeks for four to eight days. Two patients who had resections and thoracoplasties have been irregular with lengthened cycles since operation; 6 became more regular after surgery; one flowed every two weeks for three or four months and then reverted to her schedule of twenty-eight days with the flow lasting seven days. Increased flow was noted in only 2 cases. One case follows in detail:

M. R., aged 44 years, gravida 0, developed pulmonary tuberculosis in 1946, classified as far advanced on admission. The menstrual history showed that menses began at the age of 13 or 14, occurred every 28 days, and lasted 4 to 5 days. Bilateral thoracoplasty was done in 1948 and was followed by irregular menses. Streptomycin was given for 90 days. In 1949 she had two Monaldi operations and amenorrhea occurred from March to August. She received streptomycin for 50 days in 1949. From 1949 to September, 1951, menses were regular but scant. Tibione was given from September, 1951, to June, 1952, during which time she was amenorrheic. Streptomycin and PAS were started in June, 1952, and have been continued to date. After June, 1952, menses became regular again on her old schedule every twenty-nine days for four days. Menstrual pain on the third and fourth days has persisted unchanged.

The effect of artificial pneumoperitoneum on female genital physiology offers a fascinating field for speculation and it will only be by observations over a long period of time that we can determine just how serious the complications of this method of treating pulmonary tuberculosis will prove to be. Among the questions for which one would like to have answers are: What is the effect of a positive intra-abdominal pressure on the ovaries and on the process of ovulation? Is the irritating action of air sufficient to cause long-term damage to the ovaries and the physiological action of the fimbriae of the tubes at the time of ovulation? And, finally, Is the danger of causing pelvic inflammatory disease of any moment?

Among the complications of pneumoperitoneum that have been described in the literature one may mention the following: (1) abdominal discomfort or pain from pressure of the air, peritoneal irritation, and the stretching of adhesions, (2) constipation, (3) sterile peritoneal effusions, (4) peritonitis, tuberculous and nonspecific, (5) development or aggravation of hernias, (6) urinary retention, (7) dysmenorrhea, (8) pelvic inflammatory disease, (9) the production of cystoceles and rectoceles, and (10) prolapse of the

uterus.[4, 5] Banyai[6] and others have warned against the induction of pneumoperitoneum during menstruation as it may cause severe uterine cramps; refills apparently do not have this tendency. Rilance and Waring[7] found that appendicitis occurred eleven times as frequently in their patients taking pneumoperitoneum as in their sanatorium population as a whole; others have not confirmed this observation.

Twenty-six of the women in this series have had pneumoperitoneum for six months or longer; 15 of these have shown changes in their menses during that time, and in 8 of these we can, I believe, attribute the change definitely to the pneumoperitoneum. In 2 instances dysmenorrhea became much more severe after the pneumoperitoneum was established and in one of these all menstrual pain disappeared when that method of therapy was discontinued; in another case a moderately severe dysmenorrhea from which the woman had previously suffered disappeared when the pneumoperitoneum was started. One patient had profuse menses during the thirty-five months she was under treatment with pneumoperitoneum and then returned to a normal flow when the pneumoperitoneum was discontinued. The induction of the initial pneumoperitoneum caused one girl to flow for fourteen days (she then reverted to her usual twenty-day schedule lasting four to five days but with increased comenstrual dysmenorrhea) and another woman to have a single profuse period. One patient skipped two months after the induction of pneumoperitoneum and has had profuse periods since; another became irregular with lengthened intervals and with an increased number of days of flow. In one girl who had pneumoperitoneum for only two months, and therefore is not included in this series, the menses appeared every three weeks during the time the pneumoperitoneum was maintained and then returned to her normal four-week schedule when the treatment was discontinued. Another extremely interesting patient, 49 years of age and also not included in the series because she had had no periods for two years and was apparently in the menopause, spotted for three days following the induction of pneumoperitoneum.

Of the remaining 7 whose menstrual disturbances cannot be definitely traced to the pneumoperitoneum, one girl who had taken streptomycin and PAS for 19 months and pneumoperitoneum for seventeen months had normal menses until fifteen months ago when the number of days and the amount of flow began to decrease from seven to three days; for the next eight months she had periods of amenorrhea lasting one to two months, and during the past three months the number of days of flow has increased to ten to seventeen with an amount of flow that is much greater than her normal. Five other patients have shown decreased flow, one less number of days of flow, 3 increased irregularity, and one increased pain.

None of the patients in this group have, when questioned, admitted mittelschmerz although one said she had occasional shooting pains in the pelvis. One patient developed bilateral inguinal hernias which were repaired without interrupting the pneumoperitoneum but there have been no instances

of the development of cystoceles or rectoceles and none of the 26 has developed appendicitis to date. In this small group as a whole, the effect of pneumoperitoneum suggests stimulation of menstrual activity as evidenced by increased amount of flow and dysmenorrhea.

One of the most interesting developments in the field of gynecological tuberculosis in recent years has been the astonishing number of cases of endometrial tuberculosis discovered by endometrial biopsy or curettage in the routine study of sterility and the apparently successful treatment of this form of the disease and, indeed, of female genital tuberculosis as a whole by streptomycin and PAS. Available reports in the literature suggest that, as in the renal and osseous tuberculosis seen in large general hospitals, only about one-third of these patients have pulmonary lesions. While our experience with pelvic tuberculosis has been limited to patients with coexisting pulmonary disease and is too small to be of statistical value, I should like to take this opportunity of presenting certain observations and ideas for discussion.

In a review of the literature several years ago the incidence of genital tuberculosis in women dead of pulmonary tuberculosis ranged from 1 to 30 per cent.[2] Our pathologist in Saranac Lake was of the opinion that pelvic tuberculosis was rarely seen at autopsy, yet when the pelvic organs of 17 consecutive tuberculous women coming to postmortem were painstakingly examined, 6 cases with microscopic lesions were discovered. More recently O'Driscoll of Galway[11] has reported finding 6 cases in 25 women dead of pulmonary tuberculosis.

The incidence of endometrial tuberculosis in sterile women, as reported in the recent literature, varies from 5 per cent noted by Clayton[8] in England and Sharman[13] in Scotland, 8 per cent by Botella[10] in Spain, to 12.5 per cent reported by Halbrecht[9] in Palestine. Yet Israel and Meranze[12] found no endometrial tuberculosis in 177 sterile women in Philadelphia.

The diagnosis is usually made by endometrial biopsy or curettage although Halbrecht[9] was able to make the diagnosis in 28 of 530 cases by culture of the menstrual discharge and in 6 of 130 cases from the intermenstrual secretions. We tried guinea pig inoculation of menstrual blood some 18 years ago but gave it up because of the difficulty of obtaining sufficient material to inject (this was before the days of efficient culture methods) and the amount of work involved. Certainly Halbrecht's method of taking daily cultures during the menstrual period in every female patient in the sanatoria with which we are associated is out of the question, to say nothing of the amount of work the laboratory would be called upon to do. In the present series alone it would be something like four times 126, or 504 cultures a month, repeated indefinitely.

Nor does routine endometrial biopsy, which is admittedly open to serious errors of accuracy, or dilatation and curettage, either of which would have to be repeated every month if negative, appear to have much to recommend them as feasible from the economic standpoint or desirable from that of the

patient. When this study was undertaken endometrial biopsy of the included cases was considered but was given up because it was felt that, if streptomycin and PAS were as efficacious in the treatment of endometrial tuberculosis as its advocates claim, the likelihood of discovering the disease in women who had already had at least six months' treatment would be very small. The diagnosis of pelvic tuberculosis in the absence of symptoms or palpable findings, therefore, remains a problem.

It is our custom to advise curettage in every tuberculous woman who shows abnormal bleeding, yet a review of our records fails to show a single case of endometrial tuberculosis in the past five years, the period during which treatment of pulmonary tuberculosis with streptomycin and PAS has been established.

Basing our thesis, then, upon experience with other forms of tuberculosis, in which the trend is toward extirpation of the tuberculous focus whenever possible, we believe that pelvic tuberculosis associated with gross or palpable findings should be treated by radical surgery and/or low-voltage x-ray therapy and that one should not rely upon the present antibiotics to effect a cure. There is every reason to believe that the primary mortality of 9 per cent for radical surgery found in our 1935 study would be appreciably reduced today by improved pre- and postoperative care and the antibiotics.

Exhaustive studies conducted by the Veterans Administration on renal tuberculosis have shown the ineffectiveness of streptomycin against ulcerative or cavitary lesions and the necessity that lesions of sufficient extent to distort the pyelogram be removed surgically to effect a cure. The bacteriological studies of segments of lung removed after treatment with streptomycin and PAS show acid-fast bacilli in an appreciable number of instances[14] and a consideration of the pathology of tuberculosis with its relatively avascular tubercles will make one realize the impossibility of a drug, disseminated by the blood stream, reaching or having any effect on a caseous lesion. Nevertheless, according to Medlar, it is the caseous lesion which we must eradicate if the disease is to be cured.

The same difficulties are encountered in determining a cure as were noted in making a diagnosis of pelvic tuberculosis. As Halbrecht has pointed out, our methods of confirming therapeutic success or failure are limited to endometrial biopsy and to cultures from the menstrual discharge. Both methods are of value only when positive and a negative finding does not rule out the presence of tuberculosis of the endometrium nor does it give us any information about the condition of the tubes. As I have never seen a surgical or postmortem specimen of uterine tuberculosis without tubal involvement, I have yet to be persuaded that it exists.

Conclusions

The modern treatment of pulmonary tuberculosis with antibiotics, open chest surgery, and pneumoperitoneum is accompanied by all varieties of menstrual disturbances. With the exception of pneumoperitoneum, these

methods of treatment appear to suppress ovarian activity as shown by the appearance of longer cycles, fewer days of flow, and lessened amount of flow.

Therapeutic pneumoperitoneum may cause menstrual irregularities that are frequently characterized by increased flow and dysmenorrhea and that may be due to the irritating effect of the air or positive pressure on the ovaries.

The treatment of choice in tuberculosis of the female genital organs is radical removal of the diseased organs preceded and followed by a course of streptomycin and PAS or one of the isonicotinic acid derivatives. If extirpation is not feasible, low-voltage x-ray therapy given in amounts sufficient to suppress ovarian function combined with one of the antibiotics (if the organism is sensitive) will result in a higher percentage of long-term cures than will the antibiotics alone.

Pregnancy in the presence of or following proved tuberculous pelvic disease is too infrequent to weigh in the balance against the dangers of dissemination of the disease. As has been pointed out by Matthew[15] and others, mere patency of the tubes is not proof of tubal function and although the antibiotics may arrest or cure the disease and leave patent tubes, it does not follow that such tubes are capable of sufficient functional ability to produce conception.

The report of Krohn[16] that the incidence of tubal pregnancy has increased since the use of antibiotics has become widespread in the treatment of pelvic inflammatory disease should be considered in deciding whether a woman with tuberculous salpingitis should be permitted to run the risk of such an accident when there is so much to lose and so little to gain.

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Discussion

DR. N. W. PHILPOTT, Montreal, Canada.—The various upsets of menstrual function relative to pulmonary tuberculosis have been presented in an interesting and practical manner. Relationship of the various forms of treatment employed for pulmonary lesions and the disorders which occur should be of particular note to the gynecologist.

The problem of diagnosis in pelvic tuberculosis is somewhat controversial. We agree with the essayist that one can be certain that active tuberculosis is present only after bacteriologic investigation has shown positive findings. Guinea pig inoculation using endometrial scrapings has been our method of choice.

Haines of London suggests that a total curetting is more certain than the biopsy method and that there is very little added risk. May I warn that even biopsy of the endometrium where active tuberculosis is present occasionally creates complications. During the last three years we have had two patients who have sought advice in our sterility clinic. Neither one was suspected to have gential tuberculosis. Following the routine, an endometrial biopsy was performed and within a short time both individuals developed large pelvic abscesses. They were treated for many weeks with streptomycin and PAS. Needless to state, neither patient became pregnant and no cure was effected until a panhysterectomy was performed in both instances.

We are in agreement with Dr. Jameson relative to surgical treatment for those patients who have an active tuberculosis of the genital tract where there are gross findings. However, we have been open minded due to the fact that the numbers treated medically, chiefly with streptomycin and PAS, have been too small to give an accurate picture. In addition, one should be influenced by the previous mortality rates following surgery, such as the 9 per cent reported in 1935. Perhaps one should give the medical treatment first try. In some instances cure may result and, furthermore, there is the probability that this medical treatment will make subsequent surgery less hazardous. This justifies the initial medical treatment before embarking upon the rough seas of surgery.

With reference to the medical treatment, one should mention the series presented by Arthur Sutherland of Glasgow. From this large group who were proved to have genital tuberculosis, 46 were treated with streptomycin and PAS. Seven did not complete the treatment due to the fact that the disease was not arrested in 3 instances and, in the others, allergic reactions necessitated termination of treatment.

The 39 patients who completed the three months' treatment are being followed. After the lapse of one year in 10 patients, there are 3 individuals in whom the condition has definitely recurred.

May I be permitted to extend our thanks to Dr. Jameson for his informative and interesting presentation?

DR. JAMESON (Closing).—Regarding isonicotinic acid drugs, 34 women in this series had been on these drugs; none as long as six months, and that is why they were not included in the discussion. In this group there were no particular effects noted from the drugs. However, in the June 1 number of the *New York State Journal of Medicine*, there is a report by Zeichner and Childress on isonicotinic acid preparations and the authors note two cases in which the preparations were followed by suppression of the menses.

I am not really impressed by the allergic reactions to these antibiotics. It sees to me that our tuberculosis men just try to desensitize the patient and start all over again.

It is interesting to try to speculate on how these drugs affect the menstrual cycle. I do not know, but I can tell you some of our observations in a negative way. We know PAS has an effect on the prothrombin time and that the bleeding time may be increased. The pathologist at our hospital tells me that practically all of the patients who come in for chest surgery have red cells in the urine and I have seen patients with renal tuberculosis show gross hematuria when they were taking PAS. We would expect these girls to have increased bleeding, if anything, but they do not. Another observation by Brinkman of the Trudeau Sanatorium is that in 11 patients who had PAS goiter developed; 9 of the 11 were women and 4 were included in this series. We went over their records very carefully and were unable to find any particular effect that the thyroid might have had on the menstrual cycle. So I present these as negative observations.

I had hoped that someone would ask me why I think radical surgery is the treatment of choice. I feel that if anyone wants to treat these patients with antibiotics alone and set up a long-term follow-up, such as you do in carcinoma of the uterus, that would be fine; I would

like to see that. But tuberculosis is not a disease like gonorrheal salpingitis that will burn itself out; it is a relapsing disease, and I believe that as long as you have a caseous tubercle in the pelvis, you have a possible source of flare-up at any time.

I have three slides that I would like to show now. The first is a case of combined tuberculosis and carcinoma of the endometrium treated by radical surgery and with no evidence of recurrence of either disease when the patient died nearly seven years later of barbiturate poisoning. The final diagnosis was adenocarcinoma of the endometrium, Grade I, and tuberculosis of the tubes, uterus, and cervix.

The next patient was 39 years of age when first seen in December, 1939, for spotting of two months' duration. Pulmonary tuberculosis was diagnosed in 1925 at the age of 25 and she took the cure for one year. Menses appeared at 16, lasted one day, with severe cramps, no menses since. A biopsied cervical polyp revealed tuberculosis and a complete hysterectomy was done. Final diagnosis: tuberculosis of the tubes, uterus, and cervix. This patient is living and well 13 years after operation.

This last case is one I put in to show the effect of low-voltage x-ray therapy on pelvic tuberculosis. She was first seen in 1936 for a pelvic abscess. The previous history noted a pleurisy with effusion several years previously and a laparotomy at which peritoneal tuberculosis was found in 1933. A posterior colpotomy was done and a large amount of pus was evacuated. Although tubercle bacilli were not found on smear and culture was negative for secondaries, a diagnosis of pelvic tuberculosis was made. She received 10 x-ray treatments to the pelvis of low-voltage type and her general condition improved steadily. Examination in 1937 revealed a soft cystic mass the size of an orange in the right adnexal region and a smaller hard fixed mass on the left. In April, 1938, the colpotomy incision reopened and pus was evacuated. Her menstrual periods returned and continued normal. Pelvic abscesses recurred in June, 1944. Colpotomy was again done and acid-fast bacilli demonstrated. X-ray treatments were given again. The masses have gradually subsided and she has had no further pelvic symptoms. She had a cerebral thrombosis in 1951, made a good recovery, and, when I saw her a few days ago, was in good condition.

THE INFLUENCE OF ANTIBIOTIC THERAPY ON THE INTRAUTERINE BACTERIAL FLORA*†

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IN THE course of normal parturition some of the ever-present vaginal microorganisms begin their ascent into the uterine cavity. The numbers and types of organisms vary considerably. The cause of this variation stems apparently from multiple factors. Another established fact is that in an extremely high ratio the invasion becomes arrested in the uterine cavity by natural process. The exceptions represent the clinical entities of endometritis and other forms of puerperal infection. In the clinically normal patient it has not been determined whether these organisms serve a useful purpose. Such a purpose could be in a manner of débridement of the placental site and restoration of a normal endometrium.

The data which Hesseltine and Hite[7] reported before this Society in 1948 indicated that bacteria could be expected in moderate numbers until all vestiges of placental tissue had vanished and the placental sites had healed. Thus a question arises on the significance and purpose of bacterial invasion of the parturient and puerperal uterus. This question might be answered in part if it were possible to produce and maintain a sterile postpartum uterus and to correlate with this the rate of uterine involution and general welfare of the patient. If the invasion of microorganisms could not be prevented, then an alteration of the bacterial flora might yield some information on the significance of this microbiological process.

Inasmuch as antibiotics have been so extremely valuable in the treatment of puerperal infection, their administration in the early puerperium offered an avenue of exploration in conjunction with bacteriological correlation.

History

In 1861 Semmelweis[13] presented the first concrete evidence that puerperal sepsis could be highly contagious from an exogenous source. This concept of exogenous infection persisted until a few investigators documented another view on puerperal infection, namely, endogenous infection. Schottmüller[10] described an anaerobic streptococcus in 1910 which was confirmed to be pathogenic. In fact, sixteen years later, Schwarz and Dieckmann[11, 12] entered the controversy on exogenous and endogenous infection. This and their subse-

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quent reports along with the carefully documented data of Harris and Brown[5] established the endogenous concepts. Additional support came from T. K. Brown,[1] Douglas and Rhees,[3] and many others. The publications of Stone,[14] Conti, O'Laughlin, McMeans and Lipman,[2] and Holmstrom and Murata[9] illustrate some serious considerations on bacterial flora and the puerperium.

Hite, Locke, and Hesseltine[8] demonstrated synergism in experimental infections with nonsporulative anaerobic bacteria.

Various techniques have been employed for the collection of material from the uterine cavity. These transvaginal and intracervical routes have been accurate except for an occasional vaginal contamination.

Experimental Procedure

In order to keep the study as uniform and as free from error as possible, it was elected to use five common antibiotics, namely, aureomycin, Chloromycetin, penicillin, streptomycin, and terramycin and an adequate number of controls. An adequate number of controls were assured by assigning patients to each antibiotic in rotation and by using two columns for names of those in the control category. Only patients reasonably normal, who were delivered by the vaginal route without undue trauma or difficulty, were employed in the study. These stipulations and the method of treatment in rotation offered uniformity of conditions such as seasonal changes.

One further conflict which necessitated an elimination of certain cases for culture came about because of the absence of laboratory technicians on Saturdays and Sundays. Thus those patients delivered on Tuesday or Wednesday were not subjected to the collection of an intrauterine culture since the fifth day would fall on a day when the laboratory staff were absent. Possibly the resident House staff could have plated the initial media but this would have introduced a factor of bacteriologic competency. For continuity of study patients were assigned in rotation and treated accordingly even though cultures were not taken.

Patients assigned to aureomycin, Chloromycetin, streptomycin, and terramycin received these agents four times daily, namely, at 6 A.M., noon, 6 P.M., and 11 P.M. The slight irregularity at night was justified on the basis that it would disturb the patient's sleep less. Each of these were administered in 500 mg. or 0.5 Gm. amounts for a total of 2 Gm. per 24 hours. Aureomycin, Chloromycetin, and terramycin were taken orally, while streptomycin was administered by the intramuscular route.

Penicillin was given three times daily intramuscularly at 6 A.M., 2 P.M., and 10 P.M. in the amount of 400,000 units per administration or 1,200,000 units per 24 hours.

Type of Antibiotics

The oral antibiotics aureomycin and Chloromycetin were supplied in units of 250 mg. in capsules. Terramycin (amphoteric) came in the same amount in sugar-coated tablets. The aureomycin was the crystalline hydrochloride. The streptomycin was a crystalline dihydrostreptomycin as a sulfate. The

penicillin was a combination of crystalline procaine penicillin G and buffered penicillin G potassium in the ratio of 3 to 1, respectively. Thus each penicillin administration gave 300,000 units of crystalline penicillin G and 100,000 units of buffered penicillin G potassium.

Patients

Except for an occasional protest or objection by a patient, cooperation was most satisfactory. Those who objected did so because of the distress of intramuscular therapy or gastrointestinal disturbance. Aureomycin offended most frequently. All of these patients received the routine postnatal care in so far as diet, activity, lactation, showers, and like routines were concerned. The medication was started at the first scheduled period after the patient was received on the postpartum floor. Medication was given by schedule for five days. On the fifth day each patient had an intrauterine culture taken by sterile cotton applicator. The customary preparations of the vulva, upper vagina, and cervix for intrauterine culture were followed. Two sterile applicators with cotton were used for the bacteriologic specimens. These applicators were replaced in their sterile tubes and taken directly to the laboratory where transfers to the media were made. Resident physicians, specially trained, collected all culture material. Six residents collected the samples from the 665 patients. This number of patients represents the total who completed the study as instituted.

Originally some thought had been given to obtaining cultures on earlier and later dates. This would have meant reinvasion of the uterus, a procedure which might have altered the bacteriological picture.

Antibiotic Tolerance

Not one patient had any untoward reaction so far as routine cultures were concerned. One patient who had received penicillin returned a few days after she had been discharged from the hospital because of a reaction which was diagnosed by the medical service as a penicillin sensitization. The allergy-like reaction was annoying but not serious. The occurrence of flatulence and alteration of bowel habits of sufficient magnitude necessitated the discontinuance of aureomycin by some ten patients. Chloromycetin was well tolerated and in not one of the patients of the series of 102 was there evidence of reaction or intolerance as evaluated by white blood cell count. Patients on streptomycin therapy were free from unfavorable reaction aside of the local soreness at the site of the injection. Terramycin was tolerated well. Although some slight flatulence did occur, it was not necessary to interrupt the program.

In a few instances patients developed sufficient febrile reaction that other antibiotics and additional therapies were ordered. These few deletions represented approximately 2 to 3 per cent of each group. The deletion seemed necessary since the flora might be altered by the additional therapy and would not represent a true factor change.

Bacteriologic Technique

Both applicators of bacteriologic samples from each patient were properly labeled with patient's name, unit number, date, and the antibiotic employed. From this identification the technician could keep an accurate record. A technician from the laboratory accompanied by resident at the time cultures were taken from the uterus. As soon as the material reached the laboratory, two blood agar plates were streaked, one for aerobic, one for anaerobic incubation. Two tubes of dextrose brain broth, one recently boiled and cooled and one unboiled, were seeded. Anaerobiosis was produced by the vacuum and carbon dioxide flushing technique. Carbon dioxide has been a safe and inexpensive gas. This offered a satisfactory anaerobic environment. The manometer control reduced the hazard of explosion. Colonies from the plates were isolated and identified by the standard methods. Appropriate techniques were exercised in the isolation and identification of the organism found in dextrose brain broth. Diligent effort was put forth to find as many different organisms as possible in all cultures.

Most likely some anaerobic organisms were lost by the unavoidable exposure to room air and other cultural faults of aerobic atmosphere. In the instance of aerobic and anaerobic bacteria it is assumed that several strains were overgrown, outgrown, or lost in the biologic competition in the media.

Efforts were not made to test any of the organisms for antibiotic sensitization or resistance, inasmuch as the technicians' and assistants' time was fully occupied with the mere isolation and identification of the organisms.

Data

A total of 665 patients were used in this study, of whom 163 served as controls. Thus 502 patients were maintained on the antibiotic program.

Tables I to IV serve as the protocol. The number of patients in each antibiotic group was as follows: 95 for aureomycin, 102 for Chloromycetin, 103 for penicillin, 101 for streptomycin, and 101 for terramycin. The control group was stopped at the number of 163 in order to increase the numbers of the treated groups more rapidly. The over-all age range varied from 17 to 43 years and remained within normal range for each group. The average age for the control group was 22.5 while that of those on antibiotics varied from 26.2 to 27.9. This difference of the control group was entirely within the range of possibility for a series of these numbers.

Parity as used in this table counts the product of this labor. The number of children born ranges from 1 to 12 in the extremes, while in two groups the difference was from 1 to 7. The averages for all groups were almost identical. The numbers differed by only 0.3 of one child.

The establishment of the time of onset of labor is at best approximate. The use of half-hour units seemed accurate enough for the study. The duration of labor varied from one-half hour as the shortest period in 4 groups to the longest of 29½ hours in but one group. The average length of labor for all groups varied from 7 to 9 hours.

TABLE I. AGE, PARITY, LABOR, AND FETAL MATURITY

DRUG	NO. OF CASES	AGE (YEARS)		PARITY		LABOR (HOURS)		FETAL MATURITY* (PER CENT)		
		RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	PREM.	TERM	POST.
Control	163	17-42	22.5	1-12	2.2	0.5-29.5	7.5	4.9	95.0	0.0
Aureomycin	95	18-42	26.4	1-9	2.0	0.5-27.5	9.0	3.1	94.6	2.1
Chloromycetin	102	17-40	26.2	1-11	2.1	1.0-26.0	7.5	4.9	92.2	2.9
Penicillin	103	17-43	27.9	1-7	2.3	0.5-28.5	8.0	4.8	92.2	1.9
Streptomycin	101	18-40	26.3	1-7	2.1	0.5-27.5	8.0	3.0	94.0	3.0
Terramycin	101	17-38	26.5	1-8	2.2	1.5-19.5	7.0	2.9	97.0	0.0

*Premature = less than 2,500 grams.
Term = 2,500 to 4,499 grams.
Postmature = 4,500 grams and above.

TABLE II. TYPE OF DELIVERY AND MATERNAL MORBIDITY

DRUG	NO. OF CASES	DELIVERY (PER CENT)						MORBIDITY (PER CENT)		
		SPONTANEOUS	FORCEPS			BREECH	VERSION AND EXTRACTION	AMERICAN COMMITTEE STANDARD	OTHER FEBRILE INDEX	TOTAL
			OUTLET	LOW	MID					
Control	163	25.7	46.6	22.7	0.6	4.3	0	3.1	17.8	20.9
			69.3							
Aureomycin	95	25.3	44.2	25.3	3.1	2.1	0	3.2	8.4	11.6
			69.5							
Chloromycetin	102	25.5	49.0	23.5	0.0	1.9	0	1.0	10.7	11.7
			72.5							
Penicillin	103	27.2	47.6	22.3	1.0	1.9	0	2.9	14.6	17.5
			69.9							
Streptomycin	101	24.7	47.5	24.7	0.0	2.0	1	4.9	11.9	16.8
			72.2							
Terramycin	101	23.7	55.4	18.8	1.0	1.0	0	1.9	13.9	15.8
			74.2							
Total	665									

The expression of method of delivery in per cent gave a direct comparison. Spontaneous labors in the different groups were also reasonably similar. Approximately one-fourth of all deliveries were spontaneous. The difference in outlet low forceps ratio is perhaps not extreme. When the outlet and low forceps were combined the percentage range does not exceed 5 per cent with a difference of from 69.3 per cent to 74.2 per cent. The midforceps incidence, although slightly greater as expressed in multiples, is within range because of the very few cases.

Likewise the number of cases of breech as the presenting part stands out. Yet this number is too small to be significant.

The fetal maturity expressed in percentage offers an appraisal of the law of chance by assignment in rotation. The fetal ages appear to be reasonably similar. The weights of these premature newborn infants did not go below 1,900 grams and generally they are above 2,100 grams. They were all below 2,500 grams. Term maturity means fetal weight from 2,500 grams up to 4,499 grams. Postmaturity means weight over 4,500 grams.

Any therapeutic value of these drugs as prophylactic agents can be assessed under the heading of morbidity. The "American Standard" for febrile course means an elevation to 100.4° F. or 38° C. on two days, excluding the first day. Using the Standard it will be noted that the control group had a 3.1 per cent incidence of febrile morbidity, yet the Chloromycetin group had but 1 per cent, and the terramycin group had 1.9, whereas the streptomycin group went up to 4.9 per cent. Today, with better obstetrics, better management, and improved techniques, febrile courses are not as long nor as critical. Actually, because of improvements, the percentage rate of sepsis as defined by febrile course has dropped considerably.

D'Esopo,[4] in 1950, in a review of cesarean sections, introduced the idea for a simple but concrete evaluation of febrile courses, which he called "febrile index." He recommended using 99° F. as the base line. Then by adding the number of tenths of degrees above 99° for the highest reading on each day and by multiplying by ten or removing the decimal point one has a whole number. This he termed the febrile index. This can be expressed in the whole number or graphed. The elimination of the decimal point reduces confusion for some readers. Bustamante, working with us,[6] reviewed a number of records and applied the method of D'Esopo. It does give an evaluation of the group of subfebrile reactions in contrast to the American Standard rule.

This method can be made more graphic by the designation of the number of days in which there was an abnormal temperature elevation. The total for the febrile index is followed by a dash which represents the number of days of abnormal temperature course.

We agree with D'Esopo that 100.4° F. is too high for present-day evaluation, yet 99° F. seems too low.

Most standard physiological texts subscribe to 99.9° F. or 37.7° C. as the upper limit or just beyond the upper limit of normal body temperature. With these views established, D'Esopo's method was modified to this scale. The centigrade system is used at the Chicago Lying-in Hospital. This febrile index

TABLE III. AEROBIC ORGANISMS

DRUG	NO. OF CASES	FREQUENCY OF AEROBIC ORGANISMS (PER CENT)										
		STREPTOCOCCUS			STAPHYLOCOCCUS		BACILLUS					
		ALPHA (NON-FECAL)	FECAL	BETA	ALBUS	AUREUS	A. AEROGENES	E. COLI	PARACOLON	DIPHTHEROIDS	LACTOBACILLI	PROTEUS
Control	163		11.0	1.84	64.5	6.1		15.9	0.6	50.3		1.8
Aureomycin	95	4.2	3.1		83.1	5.2		13.6	3.1	23.1	1.0	15.7
			7.3									
Chloromycetin	102	7.8	10.7		85.2	5.8		5.8	0.9	24.5		5.8
			18.5									
Penicillin	103	1.9	9.7		65.0	10.7	10.6	56.3	2.9	24.2		3.8
			11.6									
Streptomycin	101	6.9	8.9		76.2	7.9		7.9		24.7		0.9
			15.8									
Terramycin	101	4.9	6.9		92.0	12.8		8.9	4.9	15.8	2.8	28.7
			11.8									

TABLE IV. ANAEROBIC ORGANISMS

DRUG	NO. OF CASES	FREQUENCY OF ANAEROBIC ORGANISMS (PER CENT)					
		STREPTOCOCCUS FACULTATIVE	STREPTOCOCCUS	MICROCOCCUS	BACTEROIDES	B. MELANINOGENICUM	B. NECROPHORUM
Control	163	15.9	52.1		44.7		0.6
Aureomycin	95	18.9	20.0		15.8		
Chloromycetin	102	21.5	37.2	0.9	21.5	0.9	0.9
Penicillin	103	13.6	23.3		16.5		
Streptomycin	101	14.8	49.5		37.6		0.9
Terramycin	101	10.9	21.7		12.8		

in the table begins at 37.8° as 0.1° since the thermometers are graduated in fifths of a degree. In Table II the febrile index does not include those cases covered by the American Standard, to emphasize the need for evaluation of those in this borderline area.

The control group had a percentage febrile by the American Standard exceeded by the aureomycin and streptomycin groups. The modified febrile index as applied to the borderline group was significantly greater in the control group than all others. If one totals these two systems a percentage follows that seems somewhat important. Comparatively, aureomycin and Chloromycetin were the most favored agents while penicillin, streptomycin, and terramycin the least protective against febrile courses but these figures must be interpreted with caution because clinical experience has shown special value of penicillin and streptomycin in puerperal infection.

Aerobic Bacteria

This study was limited to the aerobic and anaerobic bacteria recoverable by the more common cultural and technical means. Protozoa, fungi, and viri were overlooked intentionally. After careful study one cannot find a direct or immediate relationship of any two or other organisms that has any consistent occurrence pattern in accordance with present calculations. However, in contrast, there appear some relationship and correlations of bacteria to some of the antibiotics. The aerobic organisms fell into three main morphological groups: streptococci, staphylococci, and bacilli. If one wishes to add the alpha streptococcus and the *Streptococcus fecalis* together and consider all as alpha streptococci, the range is less impressive. It will be noted in the control group that streptococcus was isolated in 11 per cent. In the Chloromycetin group it was isolated in 18 per cent while in the streptomycin group in only 15 per cent. Perhaps the low of 7 per cent for aureomycin is significant. *Staphylococcus albus* was consistently high in all groups but varied considerably if not significantly. Only in those on penicillin did the number not increase. The incidence of *Staphylococcus aureus* increased in those on penicillin and terramycin therapy. It is an established fact that *E. coli* produces a penicillinase-like material. Consequently, it is not surprising that a distinct increase of this strain occurred in the penicillin group. There was a reduction in frequency of *E. coli* in those on aureomycin, streptomycin, and terramycin which may be equally noteworthy. The percentage of the paracolon group is perhaps within range. Proteus increased conspicuously under the influence of terramycin and aureomycin. *Aerobacter aerogenes* was found only in those on penicillin and at a 10+ per cent rate. The few instances of Lactobacillus offer little for comment. Diphtheroids were the second most common in the control group at 50 per cent frequency, and all five of the antibiotics appeared to produce a decided reduction in percentage incidence.

Anaerobic Bacteria

Facultative and obligate streptococci were present in all units in moderate percentage numbers. The facultative streptococcus were not greatly changed

in the over-all results. Perhaps terramycin had some influence. By contrast the obligate anaerobic streptococcus percentage rate was noticeably affected by aureomycin, penicillin, and terramycin. Bacteroides, on the other hand, were depressed significantly by aureomycin, Chloromycetin, penicillin, and terramycin. Bacteroides occurred in about 45 per cent of the control group and was reduced the lowest by terramycin to 13 per cent. Melaninogenicum was recovered and identified once. Necrophorum was found three times but only once in each of three groups.

Negative Cultures

For the sake of completion it should be added that no growth was noted in 12 cases. These were distributed in the following groups in the respective order: control 2, aureomycin 3, Chloromycetin 2, penicillin 3, and streptomycin 2. These twelve instances of "no growth" are not interpreted as sterile cavities for two of the control group had the same negative reading. These negative reports represent error in technique or loss of bacterial specimens by time, drying, or other factors well recognized in clinical bacteriology.

Comment

It should be pointed out that the uterus was in no way made sterile. Although the percentage rate of recovery was altered considerably in some instances most of the organisms found in the uterus kept reappearing.

At first glance these findings appear to contradict clinical observations and spectacular clinical responses following the administration of antibiotics for endometritis and puerperal infection. These tests were not designed to measure the total of host resistance and organism virulence and the balance of power of the antibiotics but rather the nature of microbiologic activity. These percentages do not indicate bacterial counts but only types of organisms present.

Whether greater or lesser doses of antibiotics or the institution of drugs during labor would have altered these data remains an unknown. Furthermore there was insufficient personnel to attempt studies on the possible alteration of bacterial resistance to these agents before and after therapy.

These therapeutic dosages did not keep the patients afebrile. In a few instances additional therapies were required for clinical management of cases which were removed from the study because of the combination of necessary medicaments.

Admittedly, one would like to know the degree, if any, of the bacterial floral change by combination of these antibiotics but this study did not lend itself to this particular question. From these data as well as from the original individually recorded protocol one could not with accuracy discover a combination of antibiotics to cover all aspects of the bacterial spectrum completely.

The bacterial picture presents that of the fifth postpartum day. A change might be effected by the administration of this therapy for a longer period but the evidence is yet to be uncovered.

Conclusions

It is a fact that antibiotics, other therapies, and better obstetric practices have been a major factor in the treatment of puerperal infection and in reducing puerperal sepsis deaths to a low rate. The principal offending agents of endometritis today can be, and have been fairly well controlled by our present-day antibiotics. In spite of these clinical observations, and in spite of the fact that bacteria begin their invasion of the uterus with the onset of labor and remain in considerable number for days thereafter, under the conditions of this experiment it was not possible to approximate a picture of sterility or to free the uterus completely of any one bacterium in the five days of therapy.

These patients had the accepted therapeutic dosages yet febrile courses appeared as measured by the American Standard, and by using a febrile index for the borderline cases an appreciable number could be classified as subfebrile.

A modification of D'Esopo's febrile index is recommended for concrete and specific description of febrile cases.

The cause for bacterial invasion and the nature of the bacterial population remain unanswered. What function, if any, these teeming bacteria perform remains unknown.

Except for a few instances of gastrointestinal distress, flatulence, or nausea, and the one known instance of the reaction to penicillin, there was absence of other reactions in 502 patients treated by the five common antibiotics. The white cell picture or red blood cell count remained normal in all of those receiving Chloromycetin.

Although bacteria persisted in the uterine cavity, this is not a contradiction of the value of antibiotics in clinical puerperal infection.

The question may be raised as to the possibility of one or more bacteria developing resistance to a given antibiotic, especially when administered indiscriminately, inadequately, or improperly. Thus antibiotic therapy should be administered for obvious indications. The frequency of complications due to the antibiotic remains as a significant factor.

Mrs. Anna Bauch, Joseph Lackey, and Miss Joyce Anderson rendered special technical assistance.

We acknowledge the willing and helpful cooperation of the senior and the junior staffs on all four services.

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The Lederle Laboratories Division of American Cyanamid Company, New York City, for aureomycin.

Parke, Davis & Company, Detroit, for Chloromycetin.

Merck and Company, Inc., Rahway, N. J., for both penicillin and streptomycin.

Chas. Pfizer & Co., Inc., New York, N. Y., for terramycin.

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Discussion

DR. S. A. COSGROVE, Jersey City, N. J.—The authors of this paper report a very considerable study of their objective, well conceived, acceptably carried out, and honestly discussed and evaluated.

Some of their suggestions and findings are interestingly pertinent, both to their own work and to much other more or less parallel investigation. For instance, they state that bacterial invasion of the uterine cavity is invariable, whether there is any evidence of morbid influence of such invasion or not; that it is somewhat more than conceivable that this invasion is a desirable and necessary adjuvant to the normal processes of involution and endometrial regeneration, and that possible alteration of the usual flora and the usual "balance" of various factors in the constitution of that flora might alter the hypothetical usefulness of action thereof. Indeed, their data do actually show changes in the relative pattern of the various factors in the over-all bacterial picture. It is not an unreasonable hypothesis that such changes may alter the clinical picture.

There is, in the opinion of many, a basis for some dissatisfaction with the American standard method of calculating morbidity. Moreover, it has for a long time been recognized that there are other important indications of morbidity than disturbances of the temperature pattern. The authors suggest a modification of D'Esopo's "febrile index" as a possible useful method of meeting some of the objections to the American standard. This suggestion deserves consideration, but it is perhaps questionable whether the submorbidity group defined by this method is really valid. In a consideration of morbidity it may by its inclusion in the sum total of morbidity result merely in an artificial and false statistical increase in morbidity.

This paper is necessarily and properly inconclusive. The reasons for this are indicated in the discussion of the many loopholes and loose ends inherent in it. It has great value as reliable data in the great mass of such data which must be provided by many observers along many lines before consolidation of findings can lead to useful conclusions.

We ourselves have no additions thereto to offer because we have not engaged in comparable work. Mr. Ray Chesley, head of our Department of Bacteriology, has, however, made extensive observations of vaginocervical flora in relation to the effect of "prophylactically" administered antibiotics on patients whose clinical state was conceivably jeopardized by the circumstances of labor, thus seeking to answer Hesseltine's question as to whether "the institution of drugs during labor would have altered these data," and, presumably, to determine the clinical significance of such alteration. Time will not permit discussion of Chesley's results in detail, nor are these remarks in any sense a report of his work.

He does find, however, that antibiotics given in labor do upset the proportion of the several components of the normal bacterial pattern, very importantly the marked increase in coliform organisms when penicillin is used; that there is great variability in these changes in the instance of the broad-spectrum antibiotics; and, finally, that there has been

no statistically significant improvement in clinical morbidity rates by such so-called "prophylactic" exhibition of antibiotics in labor.

Indeed, some of our data hint that morbidity incidence may have no direct relation whatever to specific bacterial patterns. Chesley has now undertaken a study of variations in complement titer to try to ascertain whether changes in this factor may not predetermine varying susceptibility to morbidity and thus develop a method of screening patients and instituting appropriate therapy when so indicated.

The continuation by many observers of investigation of the numberless facets of antibiotic therapeusis is of the greatest value and Dr. Hesseltine's present contribution deserves high appreciation.

DR. HESSELTINE (Closing).—Dr. Cosgrove could have been much more critical and this we had desired, for this work was basic and fundamental in its purpose. It is hoped that some of these data may be useful in a microbiological sense.

Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Selected Abstracts

Abortion

Heinlüffe, Von: Management of Threatened Abortion With Large Doses of Stilbestrol, Geburtsh. u. Frauenh. **12**: 1124, 1952.

There are many and different causes and disturbances, both maternal and fetal, which may result in threatened and habitual abortion. There are few and unsatisfactory treatments for these conditions, and, in the past, they have been confined to the use of bed rest, opiates and belladonna preparations, together with supplemental corpus luteum hormone and vitamin E therapy. None of these various techniques of managing threatened abortion has been very successful. Since the researches of the American workers on progesterone-estrogen levels in normal gestation, together with in vitro experiments on isolated uterine strips, evidence has been presented that, in many cases, the value of an estrogen-like preparation, stilbestrol, in large doses, would be able to prevent a threatened or imminent abortion. This type of treatment is thought to be a supplemental substitution therapy, and to be able not only to control pregnancy bleeding, but also to maintain the conceptus in the uterus.

The author, on the basis of this theory, has used large doses of diethylstilbestrol (dioxydiethyl-stilbene proprionate). The dosage schedule was as follows: 25 mg. doses were given 6 times during the first day of bleeding (total 240 mg.) or 15 mg. hourly until bleeding was under control. This was followed by the daily use of 90-100 mg.

A total of 17 cases of threatened or habitual abortion were thus treated. Of these 5 patients aborted despite therapy, the remaining 12 carrying to term and having normal healthy children. One patient delivered twins. On the other hand, one who received massive doses for 6 days spontaneously delivered a macerated fetus. The remaining patients all aborted despite intensive therapy. It is interesting to note that in those cases where the pregnancy was maintained, the amount of bleeding was "light" or minimal. The author presents these 17 cases without comment as to the efficiency of stilbestrol therapy.

L. B. WINKELSTEIN.

Cancer, Malignancies

Cuyler, W. Kenneth, Kaufmann, Louise A., Palumbo, Leonard, and Parker, Roy T.: Problems Associated With the Interpretation of Intraepithelial Carcinoma of the Cervix From Genital Smears, South. M. J. **45**: 1151, 1952.

Cytologic studies of smears made from the external cervical os provide a practical means of detecting neoplasia in the uterine cervix. Three factors affect the accuracy: the technique by which the smears are made and processed; the degree of cellular aberration; the adequacy of the histologic procedures used to affirm or negate the cytologic interpretations.

Material is obtained by aspiration rather than by one of the scraping techniques about the external cervical os. Suction is also employed to obtain material from the vaginal pool posterior to the cervix. The smears are classified cytologically into five types: I. epithelial elements apparently normal; II. abnormal but benign cellular changes; III. atypism comparable with noninvasive carcinoma; IV. elements present thought to be malignant tumor cells but scarce; V. elements present thought to be malignant tumor cells, abundant.

Cooperation between the cytologist and pathologist is essential to the final diagnosis. If the technique is going to prove useful in the diagnosis of intraepithelial carcinoma, examination of all obstetric and gynecologic patients must include a cytologic study. The smears must be prepared with careful technique and processed with skill in order to obtain a specimen which can be properly interpreted. Reliable cytologic criteria must be established for the recognition of degrees of atypism in early cervical carcinoma. When the cytology of the exfoliated cells suggests the presence of carcinoma sufficient tissue must be removed from the cervix for histologic study. The tissue specimens must be adequate and this can usually be accomplished only by a circular incision with the scalpel about the squamocolumnar junction. Punch biopsy is usually inadequate. WILLIAM BICKERS.

Endocrinology

Bernhardt, H.: Endocrine Disturbances and Interruption of Pregnancy, Medizin. Klin. **47:** 1045, 1952.

The role of the various glands of internal secretion in the normal woman is not only poorly understood, but is still less understood in the production and maintenance of gestation. There is no question but that in many cases the spontaneous interruption of pregnancy is based on the loss of endocrine balance. During the pregnancy state, many qualitative and quantitative changes occur in the ovary, the thyroid, the pituitary, the adrenals, and even in the pancreas, which changes play vital roles in the maintenance of maternal metabolism and fetal growth. Furthermore, it has been demonstrated that many of the illnesses of gestation, abortion, labor, and disturbances of the postpartum period have their pathological basis in the glands of internal secretion. It is, therefore, vital to evaluate the endocrine status, by history, physical examination, and laboratory procedures before gestation occurs, or as early as possible after the onset of pregnancy, to prevent untoward results.

However, in the judgment of the author, these endocrinopathies cannot, at least at the onset of pregnancy, be marked, because it is well known that severe endocrine disturbances most often result in primary sterility. A great deal of our glandular therapy is based on conjecture, empiricism, or superstition, with the result that more often than not failure of therapy occurs. Much experimental and clinical research must be done before the roles of the various endocrine glands in spontaneous abortion and other pathologies of pregnancy can be clearly determined. L. B. WINKELSTEIN.

Beattie, Myra K., Kay, W. W., Elton, Arnold, and Hucker, Albany G.: Masculinization Associated With Luteinized Microcysts of the Ovary, J. Obst. & Gynaec. Brit. Emp. **59:** 465, 1952.

Masculinization associated with luteinized microcysts of the ovary is of rare occurrence. Only a few cases have been reported in the literature. The authors report such a case occurring in a 21-year-old schizophrenic woman, who was admitted to the hospital after an attempt at suicide. When first seen she was hirsute and there were frank signs of virilism. The beard was thick and heavy, requiring frequent shaving. Although there were other signs of masculinity, the general shape of the body was that of a well-built woman. Long periods of amenorrhea had supervened during the past 5 years of hospitalization. The previous menstrual history was never obtainable because of her de-

pressed mental state, although she was under constant observation. Many very thorough physical examinations were performed. Extensive laboratory investigations were carried out, including x-ray of pituitary fossa, blood biochemistry and urinary steroid determinations. Although the 17-ketosteroid excretion did not indicate the presence of adrenal pathology as a cause of the virilism, laparotomy was decided upon. At operation the adrenals were found to be normal but both ovaries were polycystic. Biopsies from both ovaries were studied and because of the extensive cystic changes a bilateral oophorectomy was performed the following day. Microscopic study of these ovaries revealed "bilateral dermoid cysts with luteinized follicles and hyperplasia of theca luteal cells." Six photomicrographs illustrate the pathology found in these ovaries.

In summary, the authors state that, in the presence of normal adrenal glands with no positive evidence of pituitary hyperfunction and a regression in the masculine syndrome after bilateral oophorectomy, the etiology of the masculinization is thought to be associated with the luteinized follicle cysts of the ovaries. The mental status of the patient has remained unchanged. HARVEY B. MATTHEWS.

Gynecology

Barr, S. James: Unusual Pressure Effect of a Fibroid, J. Obst. & Gynaec. Brit. Emp. **59**: 529, 1952.

This report has to do with a case of the unusual pressure effect of a fibroid during pregnancy. The patient was a primipara, aged 26 years, married 4 years, and she had a normal prenatal course. At 37 weeks the head was high and floating and pelvic examination revealed a rather large fibroid in the posterior wall of the uterus. The tumor kept the head well out of the pelvis. Ten days before term the membranes ruptured but the fetal head remained "floating"; the cervix was long and firm and there was no labor. In view of these findings a lower segment cesarean section was performed. Mother and baby did well. Examination of the baby's skull revealed a deep depression along the entire left side of the head caused by pressure from the fibroid in the posterior wall of the uterus. X-ray examination showed no fracture along this depressed area. By the fourteenth day the baby's head had assumed its normal shape except for a slight concavity in the region of the former marked depression. At 15 months of age there was frank evidence of mental deficiency in the baby. Physically, he was well developed and normal. A short résumé of the literature is presented regarding acute deep and traumatic indentations and depressions of the fetal skull and their subsequent effects upon mental development of the child. However, nothing was found regarding such effects from long-continued pressure of two months as exemplified in the case herewith reported. In any event, a guarded prognosis as to the future mental development in these children should always be given, regardless of the etiology of the producing agent. HARVEY B. MATTHEWS.

Vara, Paavo, and Waris, Wille: Low Back Pain and Gynecological Disease, Acta obst. et gynec. Scandinav. **31**: 387, 1952.

Since patients whose chief complaint is low back pain often consult the gynecologist first, the differential diagnosis of this type of pain must be familiar to specialists in gynecology. The authors review the case histories of 200 women who consulted them with the complaint of low back pain. Only one-half (50.5 per cent) of these women had any form of gynecologic disease. In 58 per cent there were roentgen changes in the lumbosacral region. In 27 per cent of the patients, a gynecological disease was the only finding. Fifteen per cent had no abnormal findings of any objectively demonstrable type. Only 23.5 per cent showed both radiologic and gynecologic changes. One-fifth of the women had definite evidence of disc degeneration, but this was thought to represent the principal cause of the pain in only 10 per cent. The investigations undertaken on these patients unmasked 2 cases of tuberculous spondylitis. The authors conclude that patients complaining of low back pain

must be studied carefully according to a definite routine. This includes careful gynecologic examination, and roentgen examination of the pelvic girdle and lumbar spine. Obviously, such a program presupposes close cooperation between gynecologist, orthopedist, and radiologist. DOUGLAS M. HAYNES.

Szirmai, E., and Nyiri, I.: Prothrombin Changes in the Treatment of Acute and Subacute Adnexal Disease, Zentralbl. f. Gynäk. 74: 1665, 1952.

Acute and subacute infections anywhere in the body are reflected in prothrombin levels in the blood. A definite relationship has been found to exist between the amount of circulating prothrombin and acute and subacute salpingitis and parametritis. This relationship has been studied by the authors in 57 cases of acute and 32 cases of subacute adnexal disease. The bacteriological causation of the disease was not considered important. Measurements of both prothrombin time and prothrombin levels were taken before specific therapy was instituted, as well as during various periods of treatment and after treatment had been completed. Treatment of the disease was either by penicillin alone (800,000 units), penicillin (800,000 units) plus calcium (10 c.c.), streptomycin, or sulfathiazole. It was noted that the greatest degree of hypoprothrombinemia was present in the truly acute stage, and less in the subacute or chronic stage as compared to that of the normal controls. As therapy was maintained, definite increases in the prothrombin levels were noted in all cases, the degree of increase paralleling the clinical improvement. On the basis of these observations, the degree of depression of the prothrombin level could be used as an index of the degree of severity of pathology in acute and subacute adnexal disease as well as a means of differential diagnosis from other pelvic disease. Furthermore, the change in the prothrombin level could be used as a therapeutic index of the effect and efficacy of the drugs used in treatment, as correlated with the symptomatic improvements and improvement in the physical findings. L. B. WINKELSTEIN.

Kayser, H. W.: Experiences With Culdoscopy, Zentralbl. f. Gynäk. 74: 1938, 1952.

Examination of the female pelvis under direct visual conditions is a procedure which has great value in the establishment of questionable diagnosis or in the differential diagnosis of obscure female complaints. This can be accomplished by means of a peritoneoscope or by a culdoscope. The former technique has not proved as successful as the latter. The use of a direct viewing mechanism introduced into the posterior cul-de-sac was first devised and later improved upon by American workers. The author of this paper gives his experiences with 15 cases of female pelvic complaints where a definite diagnosis either could not be made or was obscure. These cases included tubal and ectopic gestation, chronic adnexal disease, sterility, endometriosis, hypertrichosis, and also seven cases where, even with the culdoscope, no definite diagnosis could be established. The ease of technique and the relative freedom from complications make culdoscopy a procedure of great value. The author concludes that he feels that culdoscopy should be a procedure in more gynecological diagnoses and that the culdoscope has a definite place in the armamentarium of the gynecologist who should perfect himself in its use. L. B. WINKELSTEIN.

Labor, Management, Complications

Kuehnel, Poul: Clinical Observations on Prolonged Labor, Acta obst. et gynec. Scandinav. 31: 413, 1952.

Kuehnel reports on the clinical aspects of 421 cases of prolonged labor, and compares them with a series of 2,734 normal cases. Prolonged labor was found to be especially frequent under the following circumstances: in primigravid women in general and in "elderly" primigravidas in particular; with unusually large baby; in patients of lean, asthenic constitution; in women of abnormally low height; and in obese patients. The risk of complications to both mother and child was much greater in cases of prolonged labor

than in labors of less than 24 hours' duration. It was Kuehnel's experience that artificial rupture of the membranes, although it did not significantly increase the duration of labor, the incidence of puerperal infection, or the maternal mortality, appeared to involve a slightly increased risk to the child and to be associated with a somewhat higher incidence of operative deliveries. Kuehnel recommends on the basis of his experience that labor be induced three to four weeks prior to term in patients whose age or constitutional characteristics make it likely that labor will be prolonged.

DOUGLAS M. HAYNES.

Dhuner, Karl-Gustav: Cardiac Irregularities Due to Trichlorethylene Given During Labor, Acta obst. et gynec. Scandinav. 31: 478, 1952.

Twenty-three patients were subjected to electrocardiographic study during labor while using trichlorethylene-air mixture as an analgesic. In the first and second stages, with trichlorethylene concentration about 0.25 per cent, arrhythmias occurred 8 times in 18 cases. During the third stage, when about 0.5 per cent trichlorethylene was given, arrhythmias occurred 13 times in 20 cases. Among 2,000 patients receiving obstetrical analgesia with trichlorethylene, 2 showed transitory signs or symptoms which might have been caused by circulatory embarrassment. Several different types of arrhythmia were observed, notably auricular and ventricular extrasystoles, bigeminal rhythm, and one case of 5:1 flutter. No clear-cut case of myocardial failure due to trichlorethylene has ever been reported, and the analgesic is to be considered a safe one, in spite of the occasional occurrence during its use of minor arrhythmias. DOUGLAS M. HAYNES.

Connell, John N., and Parsons, Milton: Brow Presentation, Bull. Margaret Hague Maternity Hosp. 5: 47, 1953.

The authors present an analysis of the persistent brow presentations which occurred during a ten-year period at the Margaret Hague Maternity Hospital. Of these there were 55 which occurred in 78,190 deliveries, or one in 1,440 deliveries.

Difficulties in diagnosis are emphasized, vaginal examination being necesasry in most instances to establish the diagnosis. Labor was prolonged by several hours except when the baby was small. Thirty and nine-tenths per cent of the women were delivered spontaneously, 43.6 per cent by low forceps, 12.8 per cent by midforceps, while 10.9 per cent were delivered by cesarean section.

There was one maternal death in the series as the result of peritonitis in association with cholelithiasis and subdiaphragmatic abscess.

There were three infant deaths, only one of which might have been the result of the presentation.

The authors emphasize the proper management of the probably prolonged labor in regard to sedation, fluids, and antibiotics prophylactically.

They state that, when the cervix is fully dilated, delivery is greatly facilitated by the use of flexion and forceps rotation.

In cases of borderline or contracted pelvis, early cesarean section is recommended. They do not feel that podalic version is a desirable procedure. KARL M. WILSON.

Newborn

Reese, Algernon B., and Blodi, Frederick C. Retrolental Fibroplasia, New York State J. Med. 52: No. 24, Dec., 1952.

This paper was presented as an introduction to a symposium on retrolental fibroplasia, and presents an outline of the proved facts in connection with the disease, one of the important causes of infant blindness.

Its incidence in premature infants is high, occurring in 65 per cent of infants weighing under 1,500 grams and in 30 per cent of infants weighing 1,500 to 2,000 grams, but it has also been observed in full-term infants, though rarely.

The pathological findings as discovered in ten pairs of eyes from affected infants dying from forty-one to one hundred days after birth are presented and are of particular interest. The disease begins in the nerve fiber layer of the retina with thickening of this layer as the result of collections of endothelial cells and an increase in the glial elements. This is followed by a breaking through of the internal limiting membrane forming masses of angiomatous tissues at first interposed between the retina and the hyaloid membrane, and which then enters the vitreous proper. This in turn is followed by hemorrhages from the newly formed vessels, later organization and contractures produce folding and detachment of the retina. The authors suggest a relationship between retrolental fibroplasia and skin hemangiomas. There is no known effective treatment. Spontaneous regression may occur in some cases. The possible value of small doses of x-ray therapy is being explored. KARL M. WILSON.

Record, R. G., Gibson, J. R., and McKeown, Thomas: Fetal and Infant Mortality in Multiple Pregnancy, J. Obst. & Gynaec. Brit. Emp. **59**: 471, 1952.

Data on fetal and infant mortality in 23,206 single births, 666 twin, 786 triplet, and 108 quadruplet births were obtained from various cities and hospitals in England, Scotland, and Wales. The fetal and infant mortality rates were 39 per 1,000 total births in single births, 152 per 1,000 in twin births, 309 per 1,000 for triplets and 509 per 1,000 for quadruplets. By comparing weights of infants at birth and number of multiple births, it was found that, at high birth weights, the mortality increases with the size of "the litter," but, at low birth weights, the mortality decreases with the size of "the litter." Only a small percentage of increase in the incidence of fetal and infant mortality can be attributed to the increase in mortality with high birth weights, as the great majority of infants in multiple births are delivered at low weights, at which mortality rates are high irrespective of the size of "the litter." The mean birth weight of infants in the single births was 7.43 pounds; in twin births 5.27 pounds, in triplet births 4 pounds, and in quadruplet births 3.07 pounds. The mean duration of pregnancy was also diminished in multiple births from 280.5 days in single births to 236.8 days in quadruplet births. These differences in weight are considered to be due in part to retardation of the growth of the fetus in the last weeks of pregnancy by "crowding" in the uterus, and in part to the early onset of labor in multiple pregnancies. HARVEY B. MATTHEWS.

Thomson, John: The Incidence of Foetal and Infant Mortality in 13,085 Births in a Maternity Hospital, J. Obst. & Gynaec. Brit. Emp. **59**: 483, 1952.

A study of the fetal and infant mortality in the booked and nonbooked cases of the Simpson Memorial Maternity Pavilion, Royal Infirmary of Edinburgh, for the years 1948 to 1951, inclusive, shows this "perinatal" mortality rate to be 49.6 per 1,000 total births in the booked group and 238 per 1,000 in the nonbooked group. An investigation of the various factors responsible for the much higher fetal and infant mortality rate in the nonbooked group showed that the only factor that had a pronounced influence was the higher incidence of immaturity of the infant in the nonbooked group. By making allowance for the different incidence of immaturity in the two groups, the perinatal mortality in the nonbooked group is reduced by 39.3 per cent for both single and twin births. It is suggested that maternity hospitals should incorporate in their reports a standardized table that shows the incidence of immaturity in single births and twins separately and in both booked and nonbooked groups; a standardized incidence of immaturity for single births might be adopted and mortality rates corrected to this standard. Such a standard would also facilitate the comparison of fetal and neonatal mortality rates in different communities or for different years in the same community. It is suggested also that maternity hospitals should include a pediatric section in their annual report, showing births in booked and nonbooked cases separately, and showing single, twin, and triplet births in each group, as well as the incidence of different birth-weight groups. HARVEY B. MATTHEWS.

Emery, J. L., and Zachary, R. B.: Hematoma of the Adrenal Gland in the Newborn, Brit. M. J. 2: 857, 1952.

The authors briefly review the reported cases of adrenal hemorrhage in the newborn. They believe the entity exists more frequently than is generally supposed because of the difficulties of clinical diagnosis in such an age group. Two cases of adrenal hemorrhage are described; one infant was explored surgically and recovered; the other died rather suddenly on the second day of life. The authors describe the pattern which seems characteristic of this entity. The infants appear normal at birth with generally no unusual event in pregnancy, during labor, or at delivery. Within a few hours (range of time, 14 hours to 5 days) the baby appears ill, takes feedings poorly, and is noted to be pale. There is always fever, often very high. The child appears restless at first and later becomes comatose. A mass is often palpable in the loin of the affected side. The authors discuss the cause of hemorrhage, questioning its relationship to trauma. The possibilities of venous thrombosis, excessive degeneration of the fetal cortex, and hemorrhagic disease are mentioned. The cause of death is usually hemorrhage and not acute adrenal insufficiency. The authors conclude that mild cases will need no therapy, but will probably not be diagnosed. Success in therapy of the severe cases demands recognition of the entity and prompt blood replacement. DONALD G. JOHNSON.

Gunn, A. L., Sutton, W. K., and Ulusoy, M.: Control of the Concentration of Oxygen in Tents for Premature Babies, Brit. M. J. 2: 1338, 1952.

Various writers have feared that too high an oxygen concentration may be harmful to premature babies. There has been the feeling that either the high concentration or the removal to lower concentrations may be a causative factor in retrolental fibroplasia. Because in most instances obstetricians and pediatricians do not know to what oxygen concentrations a baby may have been exposed, the authors have undertaken this study.

There were found to be wide variations in oxygen concentration (30 to 80 per cent) when tents in the maternity department of Lewisham Hospital, London, were checked with the flowmeters registering 1 to 2 liters of oxygen per minute. These differences were caused by the great variation in the leakage rates of tents, possibly inaccurate flowmeters, and the different-sized babies involved.

A Queen Charlotte tent was placed on a mattress with rubber and cotton sheets and a 2.8 kilogram infant. Concentrations of oxygen were checked at 5 minute intervals and it was found that a plateau was reached in 45 minutes. With flowmeter readings of 1, 2, 3, 4, and 5 L. per minute the oxygen concentration was found to be approximately 35, 38, 45, 65, and 68 per cent. Determinations were made with the B.O.C. oxygen analyzer, an instrument operating on the Pauling principle depending on the magnetic properties of oxygen, and giving an instantaneous scale reading. Nine other tents were similarly tested. Although plotted curves were alike in that they reached a constant concentration after 45 minutes, this concentration was not by any means proportional to the flow of oxygen recorded on the meter. The authors therefore concluded that the concentration can be ascertained only by analysis and the simplest method is to take a single calibration after the tent has been in operation for 45 minutes.

They further showed that if the tent is "flushed" by running the flowmeter at three times the intended rate for the first five minutes of use, the constant concentration of oxygen is reached in 30 minutes. JOHN T. COLE.

Moncrieff, Alan: Infection in the Newborn Baby, Brit. M. J. 1: Jan. 3, 1953.

The author, in delivering the Charles West Lecture before the Royal College of Physicians in London, chose the subject of "Infection in the Newborn" because of West's own interest in the subject. West was a Fellow of the Royal College of Physicians, Senior Censor, Harveian Orator, and author of the famous book, *Lectures on the Diseases*

of Infancy and Childhood. In his writings he stated that during the closing decades of the eighteenth century every sixth child born in the Dublin Lying-In Hospital died within fourteen days and "trismus" was the cause in 19 out of 20 cases. Efficient ventilating reduced the mortality, by 1833, from 1 in 6 to 1 in 58½, and only 1 in 9 was due to "trismus" (he recognized that trismus could be caused by sepsis).

Despite West's forward steps in combating infection, Cruickshank, in 1930, reported on a study of neonatal deaths, examined post mortem, of which 238 out of 800 were ascribed to infective conditions and Agnes Macgregor, in 1946, working in Edinburgh, found infection to be the cause of death in 190 out of 618 infants, or 30.7 per cent. These figures refer to the period before modern chemotherapy became available so that the incidence of infection as a cause of death is probably less today.

In none of the reports mentioned by the author is the common cold mentioned as an offender. The reasons for this omission as well as the difficulties in the diagnosis of infection in general are discussed at some length. Three charts are used to illustrate the necessity of daily temperature records, in order to evaluate properly supposedly insignificant changes, even though slight and occasionally within the range of normal.

In the discussion of special types of infection in the newborn, the classification, acquired before, during, and after birth is used. Of infections acquired before birth, congenital syphilis is listed as a completely preventable disease, if routine antenatal serological tests are conscientiously performed and treatment instituted when indicated. The matter of congenital tuberculosis and the transmission of *Bacterium coli,* malaria, and toxoplasmosis are mentioned. The effects on the unborn child of the virus diseases variola and vaccinia, as well as others, are discussed. Several case reports are given which offer evidence in support of some form of congenital serum hepatitis.

Of infections acquired during birth, inhalation plays an important part, which can be decreased to a large extent by suctioning the mouth and nasopharynx before the first breath. Gonococcal ophthalmia, although rare, is still seen and is one of the most troublesome infections in the neonatal period.

Any discussion of infections after birth brings into the picture the entire problem of immunity. Passive immunity is probably transmitted almost entirely by the placental route. As regards the development of active immunity it is still not known how quickly newborn babies can respond by antibody formation when subjected to antigenic stimulation. The practical question of whether one can, by diet, increase immunity of the newborn is raised.

Finally, the main features of infection are presented with the conclusion that any disturbance after the first few days of life should be regarded as due to infection until proved otherwise. The importance of the prevention of infection is stressed. A high standard of personal hygiene plus an adequate trained staff can achieve a great deal.

Along speculative lines, the energetic use of antibiotics and chemotherapy in the mother, in cases of premature rupture of the membranes and prolonged labor, in the hope of preventing infection in the baby is recommended. ELMER E. KRAMER.

Pregnancy Complications

Hammond, Geoffrey T.: An Inquiry Into the Treatment of Postpartum Haemorrhage, J. Obst. & Gynaec. Brit. Emp. 59: 493, 1952.

A study is presented of the mortality in 20,381 deliveries at Guy's Hospital, London, in 1928 to 1938 and 1946 to 1949 (the Obstetric Department being open only intermittently during the war). In this series, there were 56 maternal deaths; there were 7 deaths associated with postpartum hemorrhage (0.34 per 1,000), but death could not be definitely attributed to the hemorrhage in 4 of these cases; there were 3 cases in which death was attributed to the hemorrhage (0.15 per 1,000). In the management of the third stage of labor at Guy's Hospital, the patient lies on her back; a hand is placed on the fundus of the uterus, and, if there is distention, the fundus is gently compressed, and

any other manipulation of the uterus is avoided. When the placenta is separated and is in the upper vagina, it is expelled by using the uterus—then retracted—"as a plunger." Ergometrine, 0.5 mg., or Pitocin, 10 units, is then given by intramuscular injection if blood loss is excessive. If blood loss is excessive before the placenta is delivered, a Credé manual expression is done. This manual expression is first done without an anesthetic but, if it fails, a further attempt at expression is made under anesthesia. If this is unsuccessful, manual removal is done immediately; manual removal of the placenta was never done before the Credé expression method had been tried. If, at any time during these procedures, the condition of the patient deteriorates, intravenous fluid is given. In order to avoid any delay in replacing fluid, gum saline is used, and has given excellent results. Blood transfusion, if necessary, is given later. Intravenous fluid has been given in 1 of 20 patients with postpartum hemorrhage; but blood transfusion was necessary in only 1 in 50 patients. The maternal mortality rate from postpartum hemorrhage at Guy's Hospital (0.15 per 1,000) compares favorably with that reported in England and Wales, and the author concludes that there is no evidence that newer methods of treating postpartum hemorrhage are superior to "the traditional method" employed at Guy's Hospital.

HARVEY B. MATTHEWS.

Toxemia

Hallman, Niilo, and Vara, Paavo: On Fluid and Electrolyte Balance in Toxemia of Late Pregnancy, in Dehydration Caused by 10 Per Cent Salt-Free Macrodex, Acta obst. et gynec. Scandinav. 31: 462, 1952.

The authors report fluid, sodium, and potassium balance studies performed on a patient with edematous toxemia of late pregnancy after administration of 10 per cent salt-free Macrodex, a large-molecule polysaccharide similar to Dextran. By administration of this substance, it was possible to reduce the patient's weight by 5 kilograms in 7 days. Calculations performed during the balance study seemed to indicate that all the edema fluid eliminated in this way came from the extracellular fluid compartment. There were no marked fluctuations in the balance of extracellular sodium and potassium at the phase of dehydration. The results were borne out by mineral determinations for red blood cells. Immediately after birth, the child was found to have normal values for sodium, potassium, calcium, and magnesium; these elements were slightly lower in the mother than in the child.

DOUGLAS M. HAYNES.